

U.S.
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U.S. Application No.

International Application No.

PCT/JP00/01561

Attorney Docket No.

SAEG106.001APC

Date: February 22, 2002

JC05 Rec'd PCT/PTO 22 FEB 2002

**TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US)
CONCERNING A FILING UNDER 35 USC 371**

International Application No.: PCT/JP00/01561
International Filing Date: March 15, 2000
Priority Date Claimed: August 23, 1999
Title of Invention: METHOD FOR ABSOLUTE ASYMMETRIC SYNTHESIS
Applicant(s) for DO/EO/US: Hideo Nishino, Asao Nakamura and Yoshihisa Inoue

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. (X) This is a **FIRST** submission of items concerning a filing under 35 USC 371.
2. (X) This express request to begin national examination procedures (35 USC 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 USC 371(b) and PCT Articles 22 and 39(1).
3. (X) A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
4. (X) A copy of the International Application as filed (35 USC 371(c)(2))
 - a) () is transmitted herewith (required only if not transmitted by the International Bureau).
 - b) (X) has been transmitted by the International Bureau.
 - c) (X) a copy of Form PCT/1B/308 is enclosed.
 - d) () is not required, as the application was filed in the United States Receiving Office (RO/US).
5. (X) A translation of the International Application into English (35 USC 371(c)(2)).
6. (X) Amendments to the claims of the International Application under PCT Article 19 (35 USC 371(c)(3))
 - a) () are transmitted herewith (required only if not transmitted by the International Bureau).
 - b) () have been transmitted by the International Bureau.
 - c) () have not been made; however, the time limit for making such amendments has NOT expired.
 - d) (X) have not been made and will not be made.
7. (X) **Signed** Declaration and Power of Attorney of inventors (35 USC 371(c)(4)).
8. (X) A translation of the annexes, such as any amendments made under PCT Article 34, to the International Preliminary Examination Report under PCT Article 36 (35 USC 371(c)(5)).
9. (X) An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
10. (X) A **FIRST** preliminary amendment.
11. (X) A Request for Drawing Changes with figures drawings, marked in red.
12. (X) Drawing in fourteen (14) sheets.

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Page 2

13. International Application as published - face sheet only.
14. International Search Report.
15. A Verification of a Translation.
16. A return prepaid postcard.
17. The following fees are submitted:

FEES

BASIC FEE			\$890	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total Claims	4 - 20 =	0 ×	\$18	\$0
Independent Claims	1 - 3 =	0 ×	\$84	\$0
TOTAL FEES ENCLOSED			\$890	

18. A check in the amount of \$890.00 to cover the above fees is enclosed.
19. Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40 per property.
20. The Commissioner is hereby authorized to charge only those additional fees which may be required, now or in the future, to avoid abandonment of the application, or credit any overpayment to Deposit Account No. 11-1410.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:



Daniel E. Altman
Reg. No. 34,115
Customer No. 20,995

SAEG106.001APC

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant :	Nishino et al.) Group Art Unit Unknown
)
Int'l Appl. No. :	PCT/JP00/01561)
)
Int'l Filing Date:	March 15, 2000)
)
For :	METHOD FOR ABSOLUTE ASYMMETRIC SYNTHESIS)
)
Examiner :	Unknown)

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Preliminary to examination on the merits, please amend the above-captioned U.S. National Phase Application as follows:

IN THE SPECIFICATION:

Prior to the first line of the specification on page 1, please insert the following paragraph:

--This application is the U.S. National Phase under 35 U.S.C. §371 of International Application PCT/JP00/01561, filed March 15, 2000, which claims priority to Japanese Patent Application No. 11/236171, filed August 23, 1999. The International Application was published under PCT Article 21(2) in a language other than English.--

Please replace the paragraph beginning at page 8, line 13, with the following rewritten paragraph:

-- Fig. 2 (a) and Fig. 2 (b) show the calculated relationship between the optical purity: %op, conversion ratio, and the signs of the g's for the starting material (**HQ**) and the product (**HN**), in a reaction system of class (B). --

Please replace the paragraph beginning at page 8, line 17, with the following rewritten paragraph:

-- Fig. 3 (a) and Fig. 3 (b) show the calculated relationship between the optical purity (%op) of the starting material (**HQ**) or the product (**HN**), conversion ratio and K , in the reaction system of class (B). --

Please replace the paragraph beginning at page 8, line 21, with the following rewritten paragraph:

-- Fig. 4 (a) to Fig. 4 (f) show optical characteristics of (+)-**HN** and (-)-**HN**, and (+)-**HQ** and (-)-**HQ** in acetonitrile. --

Please replace the paragraph beginning at page 8, line 23, with the following rewritten paragraph:

-- Fig. 5 (a) and Fig. 5 (b) show UV and CD spectral changes by irradiation of (-)-**HN** (0.102 mM) in acetonitrile at 290 nm with LPL. --

Please replace the paragraph beginning at page 18, line 2, with the following rewritten paragraph:

-- Fig. 1 (a) and Fig. 1 (b) show that, for example, when $g = 1$ and conversion is about 50%, the optical purities (%op) of the starting material and the product are both more than 40%. -

Please replace the paragraph beginning at page 19, line 6, with the following rewritten paragraph:

-- The rate equation of the photochemical reaction in this system is represented by the following:

$$\frac{dC}{dt} = -I_{ex} \left(1 - 10^{-Abs} \right) \frac{\epsilon C}{Abs} \phi \quad (6)$$

in which C is the concentration of the reactive component; I_{ex} is the intensity of absorption light (I_0-I); Abs is the absorbance of the sample; ϵ is the molar absorption coefficient of the sample; Φ is the reaction yield; and t is the reaction time. When $Abs < 1$, equation (6) can be simplified to equation (7). --

Please replace the paragraph beginning at page 20, line 11, with the following rewritten paragraph:

-- $Abs = d(\epsilon_{QR}C_{QR} + \epsilon_{QS}C_{QS} + \epsilon_{NR}C_{NR} + \epsilon_{NS}C_{NS}) \quad (9)$

in which d is the optical path length and C is the concentration of each component ($\mathbf{HN} \equiv N$ and $\mathbf{HQ} \equiv Q$). According to the law of conservation of mass, the following relationships exist between various concentrations (C): --

Please replace the paragraph beginning at page 23, line 16, with the following rewritten paragraph:

-- Fig. 2 (a) and Fig. 2 (b) illustrate the relationship among the g , the sign of g and optical purity (%op). --

Please replace the paragraph beginning at page 24, line 2, with the following rewritten paragraph:

-- Fig. 2 (a) and Fig. 2 (b) show the optical purities (%op) of \mathbf{HQ} and \mathbf{HN} , calculated from equations (24), (25) and (26) with various values of g_Q and g_N . The following two cases (I) and (II) are shown therein: --

Please replace the paragraph beginning at page 25, line 15, with the following rewritten paragraph:

-- Fig. 3 (a) and Fig. 3 (b) show the relationship between the optical purity (%op) and K value. --

Please replace the paragraph beginning at page 25, line 17, with the following rewritten paragraph:

-- Fig. 3 (a) and Fig. 3 (b) show the results obtained from equations (24), (25) and (26), in the case of $g_Q \cdot g_N < 0$, $g_Q = -1.0$ and $g_N = 1.0$ and the case of $g_Q = 1.0$ and $g_N = -1.0$. --

Please replace the paragraph beginning at page 27, line 18, with the following rewritten paragraph:

-- \mathbf{HN} and \mathbf{HQ} were measured for their UV spectra and CD spectra (in CH_3CN). The results are shown in Fig. 4 (a) to Fig. 4 (f) together with the g values derived from these spectra. --

Please replace the paragraph beginning at page 30, line 20, with the following rewritten paragraph:

-- Fig. 6 shows changes in UV spectrum over time irradiated at 290 nm with *l*-CPL. --

Please replace the paragraph beginning at page 30, line 22, with the following rewritten paragraph:

-- The intensity of the absorption bands decreased at about 270 nm, and the UV spectrum showed two isosbestic points at 209 and 218 nm. A similar change in the UV spectrum was observed when **HN** was irradiated at 290 nm with *r*-CPL or LPL. --

Please replace the paragraph beginning at page 32, line 4, with the following rewritten paragraph:

-- The CD absorption band at about 280 nm shown in Fig. 8 (a) reflects the concentration of one of enantiomers of **HN**. The value of $\Delta\epsilon$ of (\pm) -**HQ** at 280 nm is 0. Thus the optical purity of **HN** can be determined from the value of ellipticity (θ) at 280 nm. The absorption band at about 220 nm reflects the concentration of one of enantiomers of **HQ**. In particular, because the value of $\Delta\epsilon$ of (\pm) -**HN** at 245 nm is 0, the optical purity of **HQ** can be determined using the value of θ at this wavelength. --

Please replace the paragraph beginning at page 36, line 9, with the following rewritten paragraph:

-- Therefore, **HQ** solution is irradiated with 245 nm CPL to cause absolute asymmetric synthesis. Fig. 13 (a) and Fig. 13 (b) show the relationship between the optical purity (%op) and conversion ratio which is obtained as an experimental result. In this figure, the black dots represent the results of *r*-CPL irradiation; the white dots represent the results of *l*-CPL irradiation; and the solid line represents the value calculated by simulation in which $g_Q = \pm 0.0074$, $g_N = 0$ and $K = 0.667$. --

Please replace the paragraph beginning at page 36, line 18, with the following rewritten paragraph:

-- As is apparent from Fig. 13 (a) and Fig. 13 (b), the results of experiment and simulation show good agreement. Thus, the optical purity (%op) of **HQ** increases and the optical purity (%op) of **HN** decreases as conversion ratio increases. In the photostationary state, the optical purity (%op) of **HQ** reaches a maximum and the optical purity (%op) of **HN** becomes minimal.--

Please replace the paragraph beginning at page 38, line 4, with the following rewritten paragraph:

-- Fig. 14 (a) and (b) show the relationship between the optical purity (%op) and conversion ratio as experimental data (black dots: *r*-CPL irradiation, white dots: *l*-CPL irradiation) and simulated calculation results (solid line) of **HN** in acetonitrile irradiated at 245 nm with CPL. The simulated calculation results are when $g_N = 0$, $g_Q = \pm 0.0074$ and $K = 1.5$. The

experimental results and calculated results showed good agreement. The optical purities (%op) of **HN** and **HQ** increase as conversion ratio increases. In the photostationary state, the values of these optical purities (%op) were almost equal. --

IN THE CLAIMS:

Please add new Claim 4:

4. (New) The method according to claim 1 wherein the starting material is a norbornadiene derivative and the product is a quadricyclane derivative.

IN THE DRAWINGS:

As stated in the attached Request for Approval of Drawing Changes, Applicant has requested to amend Figures 1-5, 8, 9, 13 and 14 to indicate separately each drawing, as shown in the attached copy of the figures wherein the correction is indicated with red ink.

REMARKS

Support for Claim 4 can be found in the existing specification. The specification has been amended to correct typographical errors. Additionally, drawing numbers have been amended to comply with the U.S. practice. The drawings also have been amended to comply with the U.S. practice. As such, no new matter has been added. Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE." Additionally, the cross-reference information has been included in the specification. Entry of the amendments is respectfully requested.

Should there be any questions concerning this application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Respectfully submitted,
KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: February 22, 2002

By:


Daniel E. Altman
Registration No. 34,115
Attorney of Record
620 Newport Center Drive
Sixteenth Floor
Newport Beach, CA 92660
(949) 760-0404

**VERSION WITH MARKINGS TO SHOW CHANGES MADE
IN THE SPECIFICATION:**

Paragraph beginning at line 13 of page 8 has been amended as follows:

Fig. 2 (a) and Fig. 2 (b) shows the calculated relationship between the optical purity (%op), conversion ratio, and the signs of the g's for the starting material (**HQ**) and the product (**HN**), in a reaction system of class (B).

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Fig. 1 (a) and Fig. 1 (b) show that, for example, when g = 1 and conversion is about 50%, the optical purities (%op) of the starting material and the product are both more than 40%.

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The rate equation of the photochemical reaction in this system is represented by the following:

$$\frac{dC}{dt} = -I_{ex} \left(1 - 10^{-Abs}\right) \frac{\varepsilon C}{Abs} \phi \quad (6)$$

in which C is the concentration of the reactive component; I_{ex} is the intensity of absorption light ($I_0 - I$); Abs is the absorbance of the sample; ϵ is the molar absorption coefficient of the sample; Φ is the reaction yield; and t is the reaction time. When $Abs > \leq 1$, equation (6) can be simplified to equation (7).

Paragraph beginning at line 11 of page 20 has been amended as follows:

$$Abs = d(\epsilon_{QR}C_{QR} + \epsilon_{QS}C_{QS} + \epsilon_{NR}C_{NR} + \epsilon_{NS}C_{NS}) \quad (9)$$

in which d is the optical path length and C is the concentration of each component ($HN \equiv N$ and $HQ \equiv Q$). According to the law of conservation of mass, the following relationships exist between various concentrations (C):

Paragraph beginning at line 16 of page 23 has been amended as follows:

Fig. 2 (a) and Fig. 2 (b) illustrates the relationship among the g, the sign of g and optical purity (%op).

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Fig. 2 (a) and Fig. 2 (b) shows the optical purities (%op) of HQ and HN, calculated from equations (24), (25) and (26) with various values of g_Q and g_N . The following two cases (I) and (II) are shown therein:

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Paragraph beginning at line 17 of page 25 has been amended as follows:

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Paragraph beginning at line 18 of page 27 has been amended as follows:

HN and **HQ** were measured for their UV spectra and CD spectra (in CH₃CN). The results are shown in Fig. 4 (a) to Fig. 4 (f) together with the *g* values derived from these spectra.

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Paragraph beginning at line 22 of page 30 has been amended as follows:

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Paragraph beginning at line 9 of page 36 has been amended as follows:

Therefore, **HQ** solution is irradiated with 245 nm CPL to cause absolute asymmetric synthesis. Fig. 13 (a) and Fig. 13 (b) shows the relationship between the optical purity (%op) and conversion ratio which is obtained as an experimental result. In this figure, the black dots represent the results of *r*-CPL irradiation; the white dots represent the results of *l*-CPL irradiation; and the solid line represents the value calculated by simulation in which $g_Q = \pm 0.0074$, $g_N = 0$ and $K = 0.667$.

Paragraph beginning at line 18 of page 36 has been amended as follows:

As is apparent from Fig. 13 (a) and Fig. 13 (b), the results of experiment and simulation show good agreement. Thus, the optical purity (%op) of **HQ** increases and the optical purity

(%op) of **HN** decreases as conversion ratio increases. In the photostationary state, the optical purity (%op) of **HQ** reaches a maximum and the optical purity (%op) of **HN** becomes minimal.

Paragraph beginning at line 4 of page 38 has been amended as follows:

Fig. 14 (a) and (b) shows the relationship between the optical purity (%op) and conversion ratio as experimental data (black dots: *r*-CPL irradiation, white dots: *l*-CPL irradiation) and simulated calculation results (solid line) of **HN** in acetonitrile irradiated at 245 nm with CPL. The simulated calculation results are when $g_N = 0$, $g_Q = \pm 0.0074$ and $K = 1.5$. The experimental results and calculated results showed good agreement. The optical purities (%op) of **HN** and **HQ** increase as conversion ratio increases. In the photostationary state, the values of these optical purities (%op) were almost equal.

IN THE CLAIMS:

New Claim 4 has been added.

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022102

SAEG106.001APC

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant :	Nishino et al.) Group Art Unit Unknown
)
Int'l Appl. No. :	PCT/JP00/01561)
)
Int'l Filing Date:	March 15, 2000)
)
For :	METHOD FOR ABSOLUTE ASYMMETRIC SYNTHESIS)
)
Examiner :	Unknown)

REQUEST FOR APPROVAL OF DRAWING CHANGES

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Pursuant to 37 C.F.R. § 1.123, Applicant requests approval of the following drawing changes shown in red on the attached copies of Figures 1-5, 8, 9, 13 and 14:

In Figure 1, please replace drawing numbers (a) and (b) with drawing numbers Fig. 1 (a) and Fig. 1 (b), respectively.

In Figure 2, please replace drawing numbers (a) and (b) with drawing numbers Fig. 2 (a) and Fig. 2 (b), respectively.

In Figure 3, please replace drawing numbers (a) and (b) with drawing numbers Fig. 3 (a) and Fig. 3 (b), respectively.

In Figure 4, please replace drawing numbers (a), (b), (c), (d), (e) and (f) with drawing numbers Fig. 4 (a), Fig. 4 (b), Fig. 4 (c), Fig. 4 (d), Fig. 4 (e) and Fig. 4 (f), respectively.

In Figure 5, please replace drawing numbers (a) and (b) with drawing numbers Fig. 5 (a) and Fig. 5 (b), respectively.

In Figure 8, please replace drawing numbers (a) and (b) with drawing numbers Fig. 8 (a) and Fig. 8 (b), respectively.

In Figure 9, please replace drawing numbers (a) and (b) with drawing numbers Fig. 9 (a) and Fig. 9 (b), respectively.

In Figure 13, please replace drawing numbers (a) and (b) with drawing numbers Fig. 13 (a) and Fig. 13 (b), respectively.

In Figure 14, please replace drawing numbers (a) and (b) with drawing numbers Fig. 14 (a) and Fig. 14 (b), respectively.

REMARKS

The amendment to the drawings requested herein is for designating separately each drawing. The amendment does not raise any new matter, and Approval of this amendment is respectfully requested.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

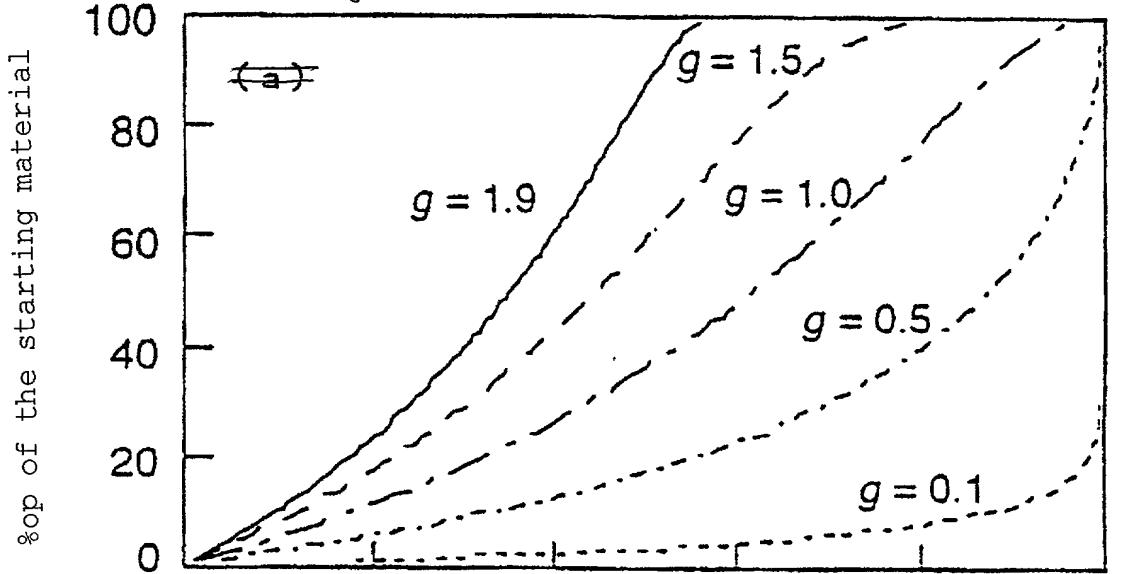
Dated: February 22, 2002 By:



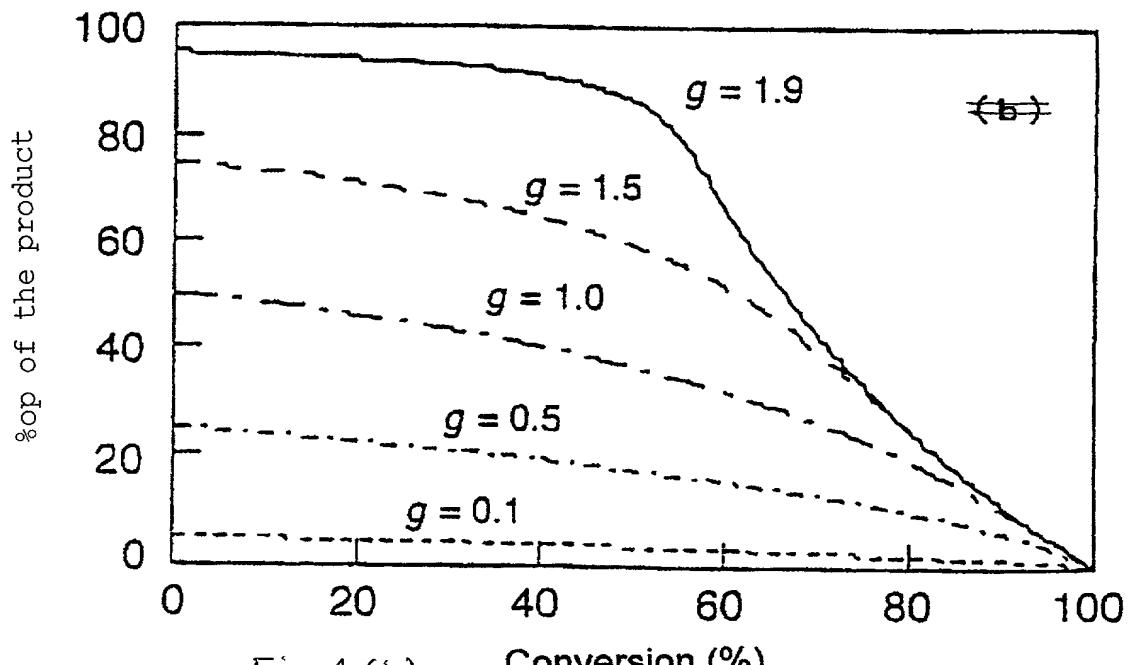
Daniel E. Altman
Registration No. 34,115
Attorney of Record
620 Newport Center Drive
Sixteenth Floor
Newport Beach, CA 92660
(949) 760-0404

Fig. 1

Fig. 1(a)



(a)



(b)

Fig. 1 (b)

Fig. 2

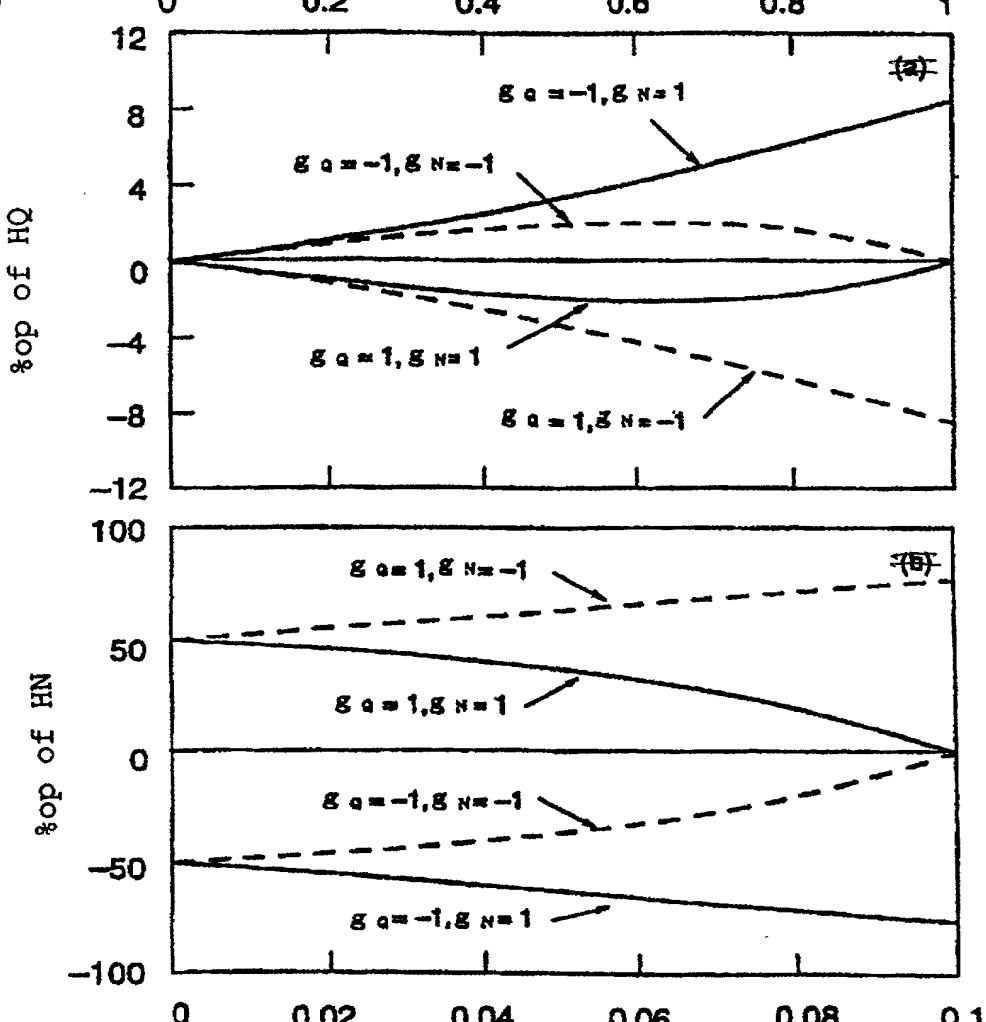
Fig. 2(a) $[HN]/(\text{concentration of HN in the photostationary state})$ 

Fig. 2(b)

$$[HN] / ([HN] + [HQ])$$

~~Fig. 3~~

Fig. 3(a)

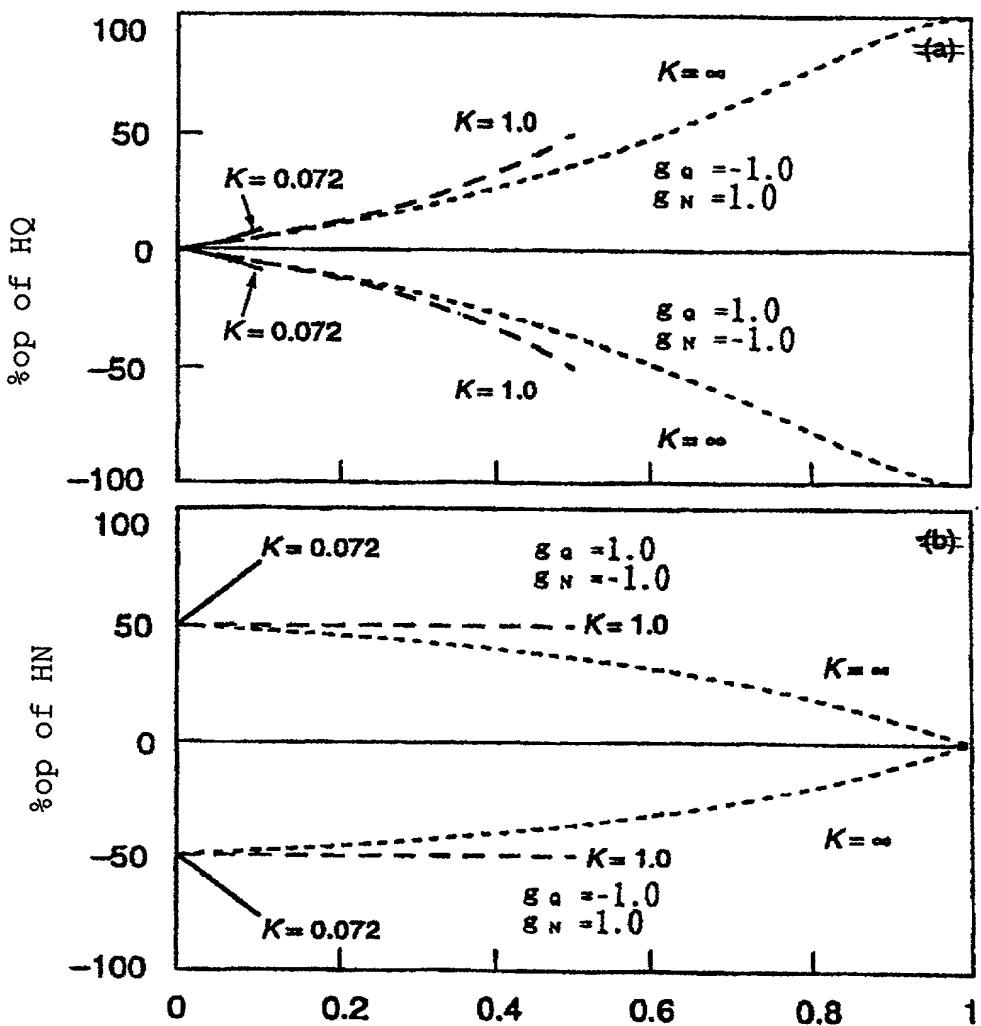


Fig. 3(b)

% op of HN

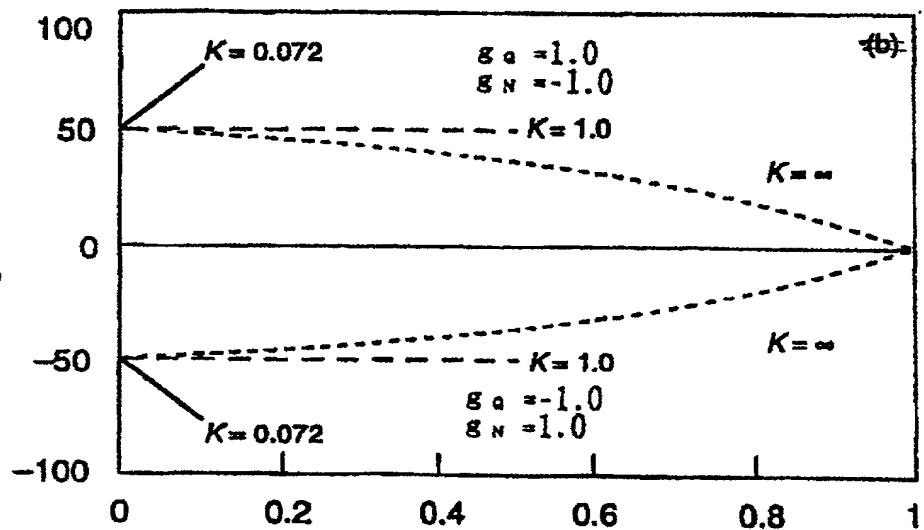


Fig. 3(b)

$$[\text{HN}] / ([\text{HN}] + [\text{HQ}])$$

~~Fig. 4~~

Fig. 4(a)

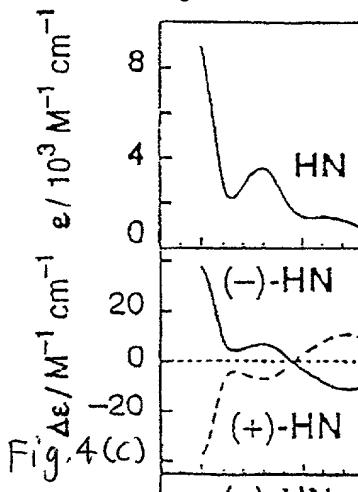


Fig. 4(b)

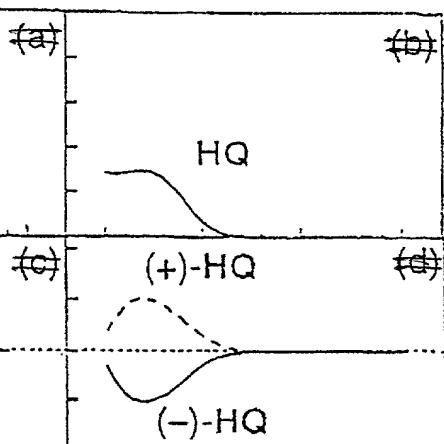


Fig. 4(d)

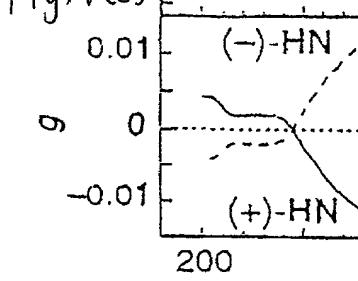


Fig. 4(e)

Wavelength (nm)

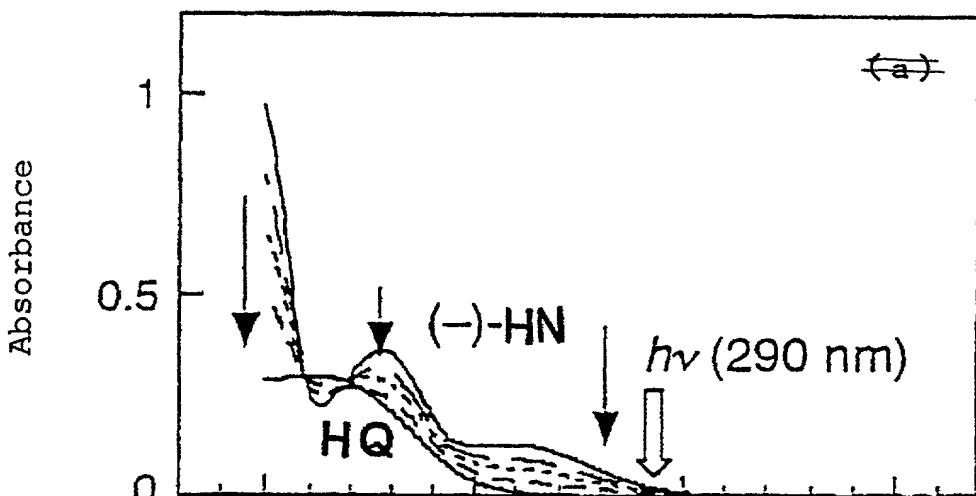


Fig. 4(f)



~~Fig. 5~~

Fig. 5(a)



Absorbance

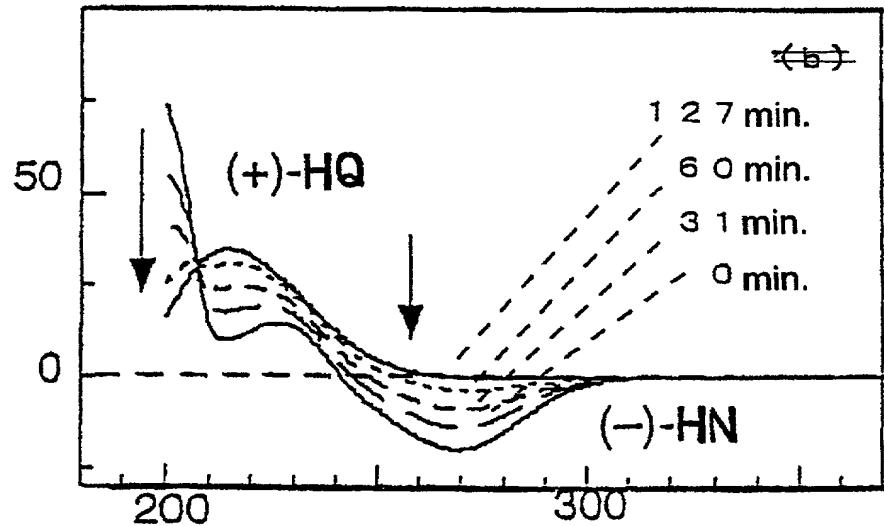
 θ (mdeg)

Fig. 5(b)

Wavelength (nm)

Fig. 8

Fig. 8(a)

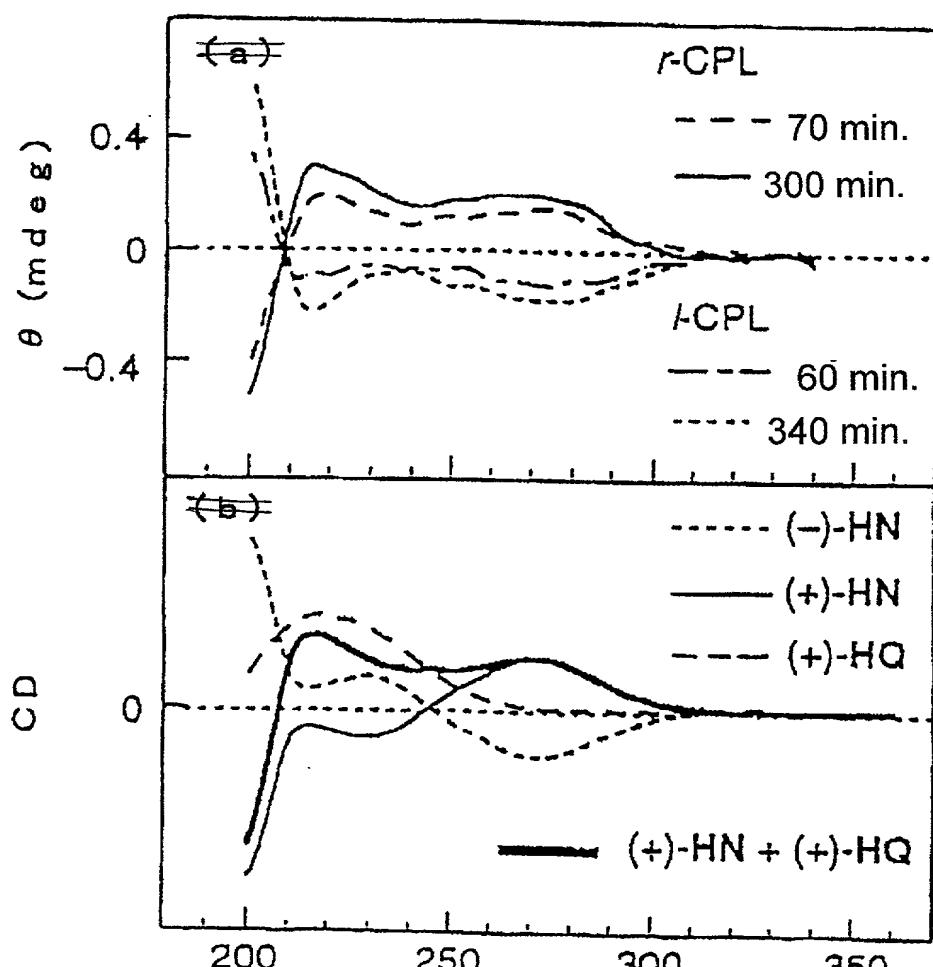
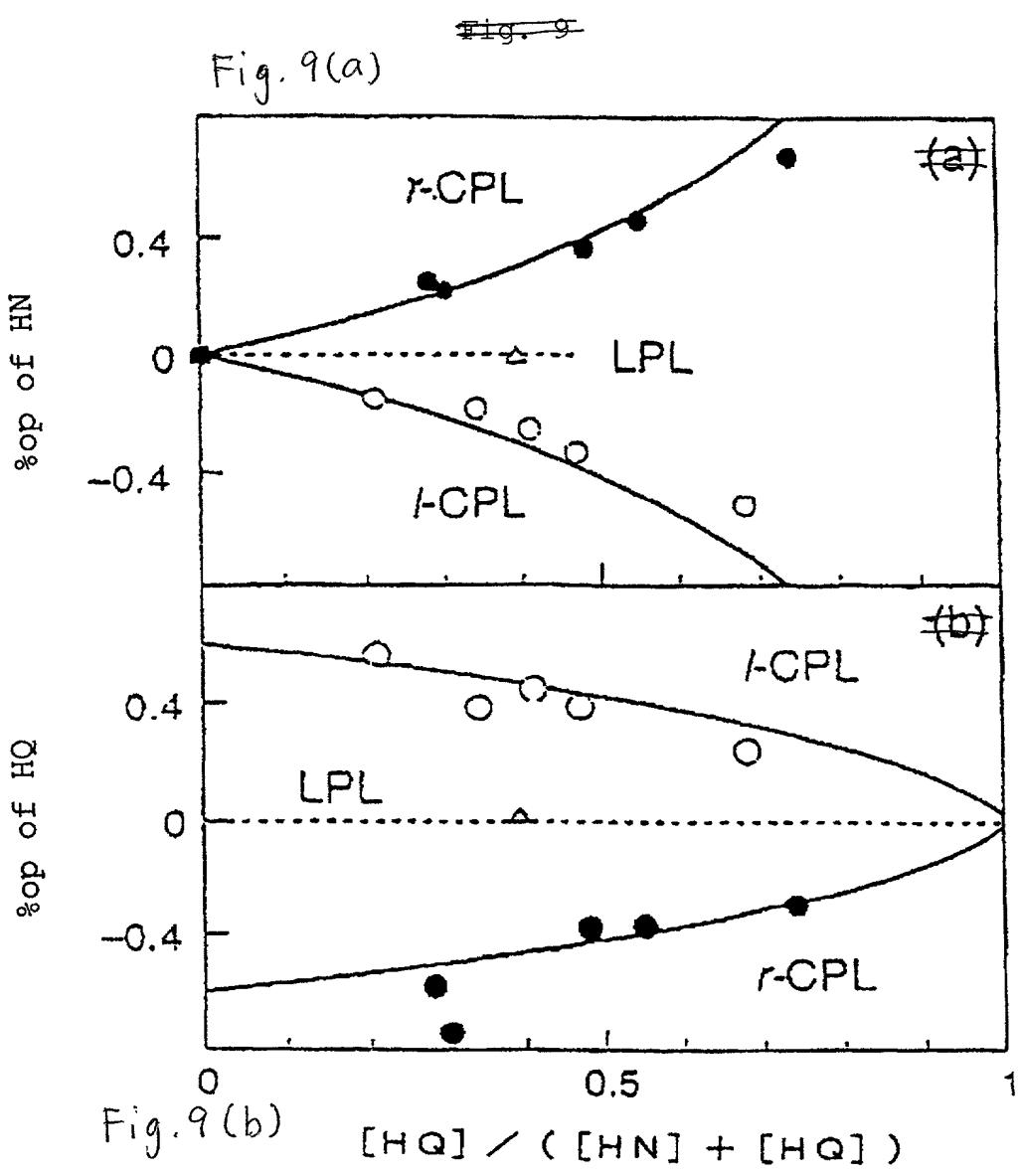


Fig. 8(b)

Wavelength (nm)



~~Fig. 13~~

Fig. 13(a)

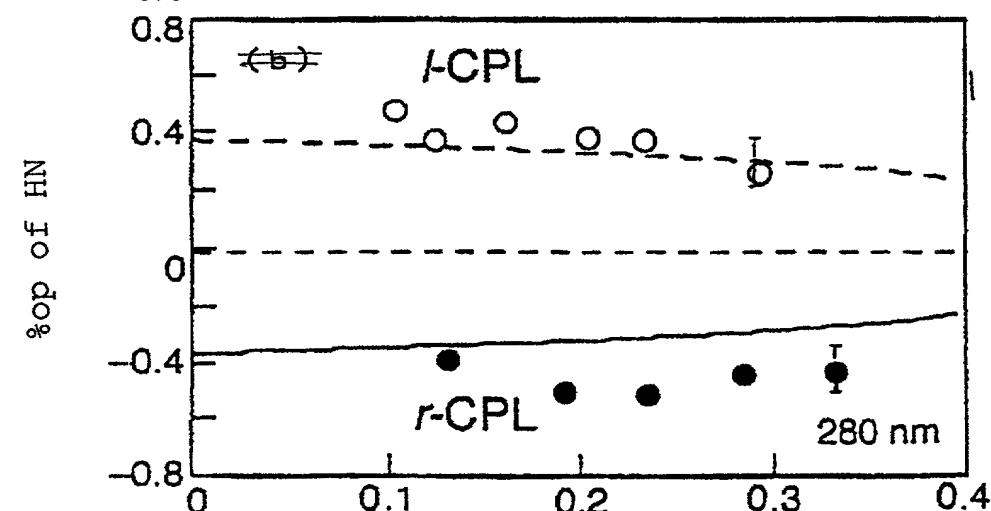
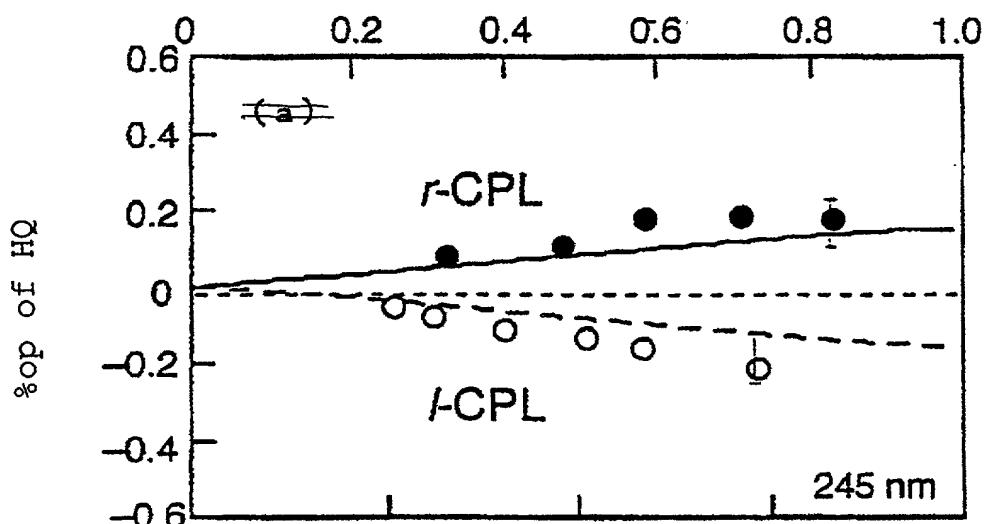
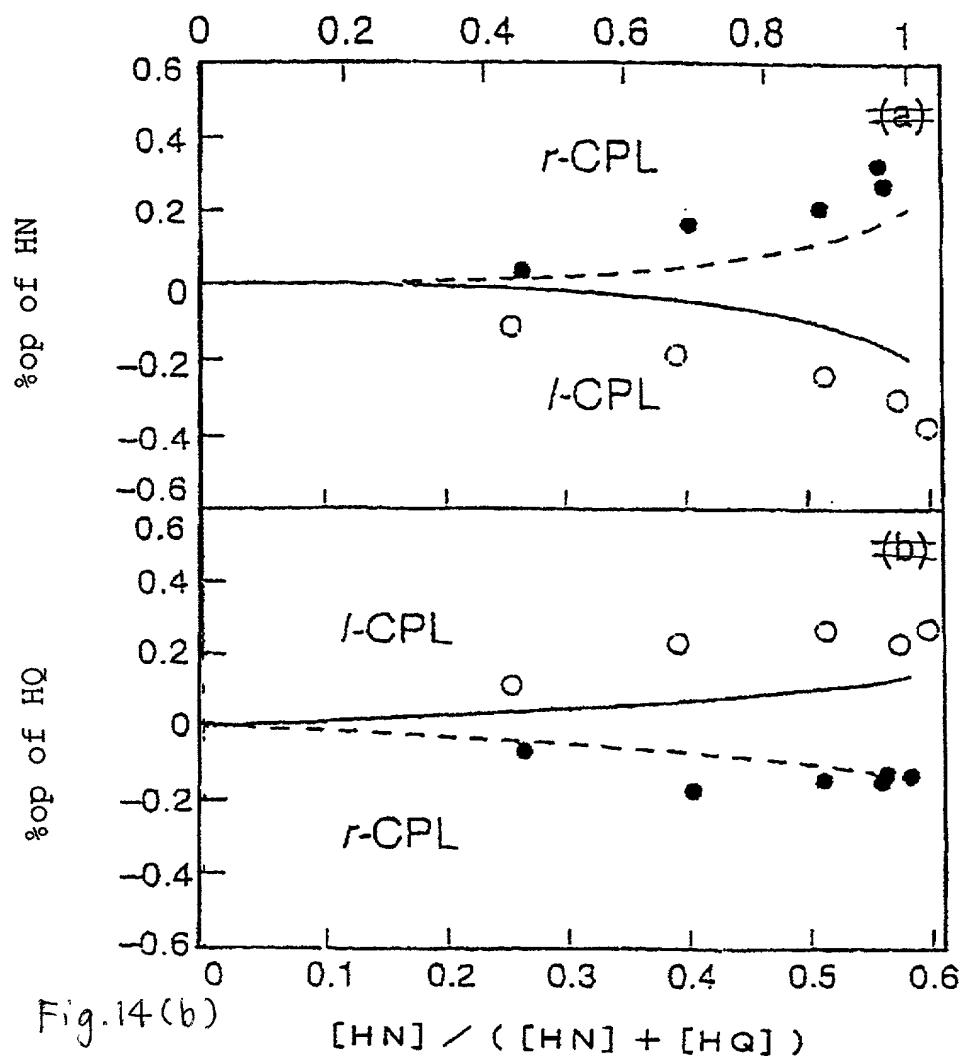
Fig. 13(b) $\frac{[HN]}{[HN] + [HQ]}$

Fig. 14(a)

[HN]/(concentration of HN in the photostationary state)

Fig. 14



SAEG106.001APC

14/parts

PATENT

-1-

DESCRIPTION

METHOD FOR ABSOLUTE ASYMMETRIC SYNTHESIS

5 TECHNICAL FIELD

The present invention relates to a method for absolute asymmetric synthesis. More specifically, the invention relates to a novel method for absolute asymmetric synthesis, which enables concentration of one 10 of the enantiomers or diastereomers in the starting material and one of the enantiomers or diastereomers in the product, in a reaction system in which the enantiomers or diastereomers are not converted into each other chemically or thermally.

15

BACKGROUND ART

Asymmetric synthesis plays an important role in the preparation of various optically active chemicals, such as pharmaceuticals, agricultural chemicals, perfumes, 20 cosmetics, and intermediates thereof. In the second half of the nineteenth century, the usefulness of right- and left-circularly polarized light (r-CPL and l-CPL) was confirmed by van't Hoff. Since then, there have been many attempts to produce optically active chemicals using 25 circularly polarized light (CPL).

Such synthesis of optically active chemicals using CPL is one type of "absolute asymmetric synthesis" (AAS). That is, asymmetric induction is realized by preferential excitation of one of the enantiomers by means 5 of irradiation with right- or left-circularly polarized light. The anisotropic factor, also known as "g", is considered to determine the degree of selective excitation. The anisotropic factor g was defined by Kuhn as the difference between optical isomers in molar absorption 10 coefficient for *r*- or *l*-CPL at a certain wavelength as follows:

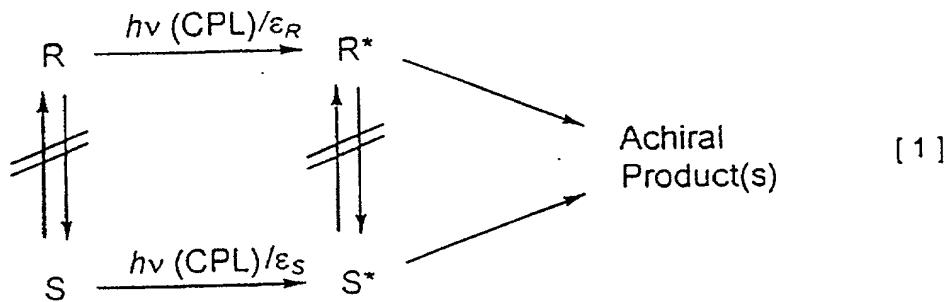
$$g = (\varepsilon_l - \varepsilon_r) / \varepsilon = \Delta\varepsilon / \varepsilon \quad (1)$$

in which $\varepsilon = (\varepsilon_l + \varepsilon_r) / 2$ and $0 \leq g < 2$ (*Trans. Faraday Soc.* 1930, 293-309; *Z. Phys. Chem., B. Abt.* 1930, 7, 292-15 310).

Absolute asymmetric synthesis (AAS) is classified into three categories: (a) asymmetric photolysis, (b) photochemical deracemization and (c) photochemical asymmetric fixation.

20 In asymmetric photolysis, the two enantiomers in the starting material are photochemically decomposed in different extents depending on the degree of their selective excitation by irradiation with *r*- and *l*-CPL at a certain wavelength. Scheme [1] shows this asymmetric 25 photolysis.

-3-

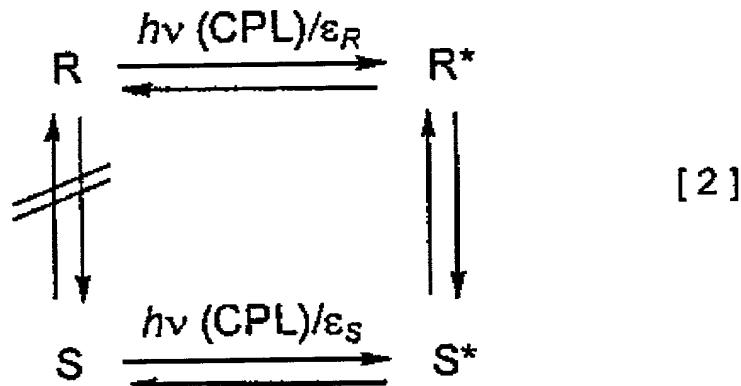


In place of ϵ_1 and ϵ_r , ϵ_R and ϵ_s are used herein.

ϵ_R and ϵ_s represent molar absorption coefficients of the
5 two enantiomers for *r*-CPL or *l*-CPL, respectively. The
enantiomer less excited by *r*- or *l*-CPL remains in the
starting material and the optical purity is increased,
whereas the other enantiomer decomposes. In this type of
absolute asymmetric synthesis, the photochemical process
10 is irreversible. There are many reports on such
asymmetric photolysis. Representative examples are a
report on photolysis of camphor (*Z. Phys. Chem., Abt. B*,
1930, 292-310) and a report on photolysis of trans-
bicyclo[4,3,2]nonan-8-one (*J. Chem. Soc., Chem. Commun.*
15 1978, 983-4).

Scheme [2] shows a photochemical deracemization process. As shown in Scheme [2], the total concentration of the enantiomers does not change during the photoreaction. Preferential excitation of one enantiomer
20 over the other photochemically shifts the equilibrium, and

the enantiomer ratio is fixed upon termination of irradiation. However, except for inorganic compounds (*Mol. Photochem.* 1969, **1**, 271; *Chem. Commun.* 1996, 2627-2628), there are only a few reports of photochemical deracemization. Organic compounds, which exclusively undergo photoderacemization, have been rarely reported. Actually, it appears that side reactions always occur when organic compounds are photochemically deracemized.

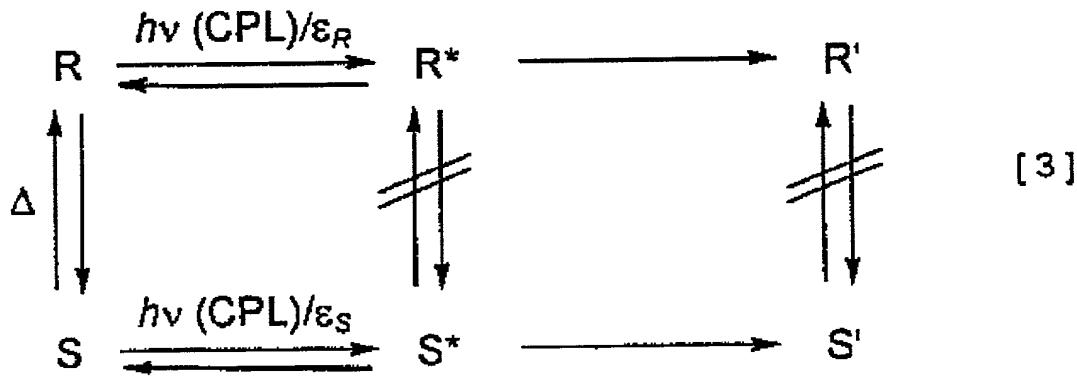


10

The photochemical process of asymmetric fixation resembles asymmetric photolysis. In the process, the starting material undergoes thermal racemization and as shown in Scheme [3], an enantiomer-selective photoreaction is induced by irradiation with *r*- or *l*-CPL and thereafter an optically active product is obtained.

15 The *R/S* ratio of the product is equal to the molar absorption coefficient ratio, ϵ_R/ϵ_S . There are not many

examples of such photochemical asymmetric fixation. This type of photochemical asymmetric fixation includes, for example, oxidative photocyclization of 1-(2-benzo[c]phenanthryl)-2-phenylethylene to hexahelicene via dihydrohericene (*J. Am. Chem. Soc.* 1971, **93**, 2553; *J. Am. Chem. Soc.* 1973, **95**, 527-32).



The reversible absolute asymmetric synthesis of 1,1'-binaphthyl pyran recently proposed by G.B. Schuster, et al. is a variation of photochemical deracemization (*J. Am. Chem. Soc.* 1998, **120**, 12619-12625).

As shown above, conventional methods for absolute asymmetric synthesis using circularly polarized light are methods for obtaining, in the starting material, an excess amount of one enantiomer relative to the other primarily by utilizing preferential decomposition or shifting the enantiomer ratio by means of irradiation with circularly polarized light.

Under the circumstances described above, the present invention was made. The present invention focuses on the reaction product to which none of the conventional researchers have paid attention. An object of the present
5 invention is to provide a novel method for absolute asymmetric synthesis, which enables concentration of one of the enantiomers or diastereomers in the starting material and one of the enantiomers or diastereomers in the product, in a reaction system in which the enantiomers
10 or diastereomers (i.e., *R*-isomer and *S*-isomer relative to one asymmetric carbon) are not chemically or thermally converted into each other.

DISCLOSURE OF INVENTION

15 To achieve the above object, the present invention provides the following inventions:

First, the present invention provides a method for synthesizing absolute asymmetry which comprises: providing a photochemically reversible reaction system in
20 which the starting material is a mixture of enantiomers or diastereomers not photochemically or thermally converted into each other; and irradiating the reaction system with right- or left-circularly polarized light to excite the starting material alone or both the starting material and the product,

thereby concentrating one of the enantiomers or diastereomers in the starting material and one of the enantiomers or diastereomers in the product that corresponds to the enantiomer or diastereomer not concentrated in the starting material.

Secondly, the present invention provides the above method in which the starting material and the product are mixtures of enantiomers and only the starting material is excited, the concentration of one of the enantiomers in the starting material and one of the enantiomers in the product being controlled by adjusting the anisotropic factor g , which indicates the degree of selective excitation by right- and left-circularly polarized light.

Thirdly, the present invention provides the above method in which the starting material and the product are mixtures of enantiomers and both the starting material and the product are excited, the concentration of one of the enantiomers in the starting material and one of the enantiomers in the product being controlled by adjusting at least one of the following:

the value of anisotropic factor g which indicates the degree of selective excitation by right- and left-circularly polarized light;

plus or minus sign of g ; and

K indicating the photochemical equilibrium of the reaction.

BRIEF DESCRIPTION OF DRAWINGS

5 Fig. 1 (a) shows the relationship between the optical purity (%op) of the starting material and conversion by CPL irradiation, corresponding to different values of *g* for the starting material, in a reaction system of class (A); and Fig. 1 (b) shows the relationship
10 between the optical purity (%op) of the product and the conversion by CPL irradiation, corresponding to different values of *g* for the starting material.

Fig. 2 shows the calculated relationship between the optical purity: %op, conversion ratio, and the signs
15 of the *g*'s for the starting material (**HQ**) and the product (**HN**), in a reaction system of class (B).

Fig. 3 shows the calculated relationship between the optical purity (%op) of the starting material (**HQ**) or the product (**HN**), conversion ratio and *K*, in the reaction
20 system of class (B).

Fig. 4 shows optical characteristics of (+)-**HN** and (-)-**HN**, and (+)-**HQ** and (-)-**HQ** in acetonitrile.

Fig. 5 shows UV and CD spectral changes by irradiation of (-)-**HN** (0.102 mM) in acetonitrile at 290 nm
25 with LPL.

Fig. 6 shows UV spectral changes by irradiation with 290 nm CPL.

Fig. 7 shows the relationship between irradiation time and the conversion of **HN** solution 5 irradiated at 290 nm with CPL and LPL.

Fig. 8 (a) shows CD spectral changes by irradiation of **HN** acetonitrile solution at 290 nm with *l*- and *r*-CPL. Fig. 8 (b) shows calculated CD spectrum of (+)-**HN** and (-)-**HN** irradiated with 290 nm *r*-CPL.

10 Fig. 9 (a) shows the relationship between the optical purity (%op) of the starting material (**HN**) and conversion ratio. Fig. 9 (b) shows the relationship between the optical purity (%op) of the product (**HQ**) and conversion.

15 Fig. 10 shows UV spectral changes in **HQ** solution irradiated at 245 nm with *l*-CPL.

Fig. 11 shows CD spectral changes in **HN** solution irradiated at 245 nm with *l*-CPL and *r*-CPL, respectively. The CD spectra were measured after dilution to 0.29 mM 20 ($[HQ]_0=0.87$ mM).

Fig. 12 shows a simulated calculation of CD spectral changes in **HQ** irradiated at 245 nm with *r*-CPL.

Fig. 13 shows a simulated calculation and experimental data of **HQ** excited by CPL irradiation (245 nm). Fig. 13 (a) shows the relationship between the 25

optical purity (%op) of the starting material (**HQ**) and conversion. Fig. 13 (b) shows the relationship between the optical purity (%op) of the product (**HN**) and conversion.

5 Fig. 14 shows a simulated calculation and experimental data of **HN** excited by CPL irradiation (245 nm). Fig. 14 (a) shows the relationship between the optical purity (%op) of the starting material (**HN**) and conversion ratio. Fig. 14 (b) shows the relationship
10 between the optical purity (%op) of the product (**HQ**) and conversion.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention has the features described
15 above. Preferred modes for carrying out the invention will be described below.

The method for synthesizing absolute asymmetry according to the first embodiment of the invention comprises:

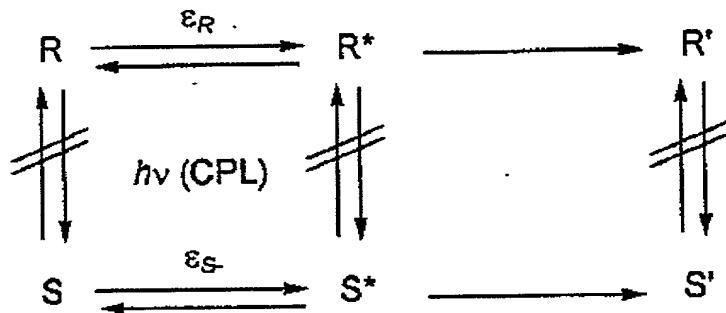
20 providing a photochemically reversible reaction system in which the starting material is a mixture of enantiomers or diastereomers not photochemically or thermally converted into each other; and
irradiating the reaction system with right- or left-
25 circularly polarized light to excite the starting material

alone or both of the starting material and the product,
thereby concentrating one of the enantiomers or
diastereomers in the starting material and one of the
enantiomers or diastereomers in the product (or achieving
5 further concentration of one of the enantiomers or
diastereomers in the starting material and/or the product,
if already concentrated). The photochemically reversible
system includes a reaction reversible by irradiation with
the same kind of light at the same wavelength, and a
10 reaction reversible by irradiation with a different kind
of light or with the same kind of light but at a different
wavelength.

The mixture of enantiomers includes a racemic
mixture that is an equivalent mixture. Diastereomers can
15 also be used in the invention because they can be
considered as an *R*-isomer or an *S*-isomer, relative to one
asymmetric carbon in the molecular structure, for example,
in the case of no interaction between asymmetric centers.

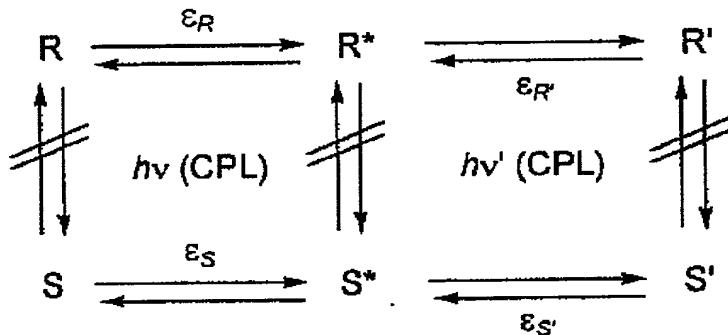
Optically reversible reaction systems can be
20 classified into two classes shown in Scheme [4].

Class (A)



[4]

Class (B)



In class (A), only the starting material is excited with circularly polarized light (CPL) and the product is not excited. In class (B), both the starting material and the product are excited.

5 A representative example of the starting material-product reaction system of the present invention is a norbornadiene derivative-quadracyclane derivative system.

However, the kinds of starting material and product in the absolute asymmetric synthesis method of the present invention are not specifically limited.

- Norbornadiene and quadricyclane have been
- 5 investigated in detail because photoisomerization from norbornadiene to quadricyclane has potential for solar energy storage. Quadricyclane is a thermally stable compound and classified structurally as a highly distorted cyclobutane derivative. Quadricyclane can be
- 10 photochemically synthesized via [2+2] intramolecular cycloaddition of photochemically excited norbornadiene. It is also possible to produce norbornadiene by the reverse reaction, i.e., photochemical or thermal reaction of quadricyclane.
- 15 The photoisomerization between chiral norbornadiene derivatives and quadricyclane derivatives formed by introduction of asymmetric substituents is a reaction system in which enantiomers or diastereomers are not photochemically or thermally converted into each other.
- 20 This photoisomerization is an example of the absolute asymmetric synthesis method of the invention which enables concentration of one of the enantiomers or diastereomers in the starting material and one of the enantiomers or diastereomers in the product by irradiation with
- 25 circularly polarized light (CPL).

Interestingly, it is not widely known that norbornadiene and quadricyclane have a prochiral structure. There are only a few reports describing the optical properties of chiral norbornadiene derivatives. As far as 5 the present inventors know, there has been no report on the optical properties of chiral quadricyclane derivatives. In addition, no systematic investigation has been carried out on photochemical conversion between chiral norbornadiene and quadricyclane. Therefore, the 10 stereochemical consequences of the photocyclization have yet to be clarified.

Of course, the present invention is not limited to the norbornadiene derivatives-quadricyclane derivatives system.

15 As mentioned above, in various starting material-product reaction systems, the method of the present invention enables concentration of one of the enantiomers or diastereomers in the starting material and one of the enantiomers or diastereomers in the product.

20 In class (A) and class (B) shown in Scheme [4], the present invention enables efficient concentration of one of the enantiomers in the starting material and one of the enantiomers in the product, in a highly controlled manner.

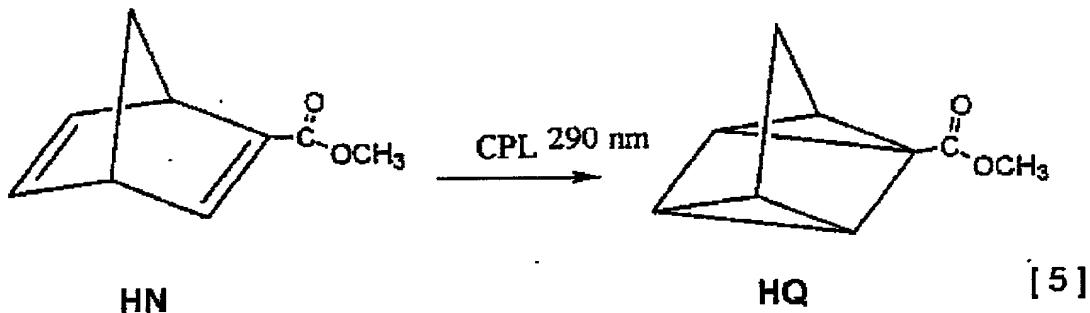
25 Classes (A) and (B) will be described in order

below.

Class (A)

In class (A), as described in the second embodiment of the invention, the starting material and the product are mixtures of enantiomers and only the starting material is excited. One of the enantiomers in the starting material and one of the enantiomers in the product are concentrated by controlling the anisotropic factor g which indicates the degree of selective excitation of the starting material by right- and left-circularly polarized light. The g can be controlled by application of Kagan's equation shown below.

Examples of class (A) include the norbornadiene derivative-quadracyclane derivative system shown in Scheme 15 [5].



In this reaction system, when methyl bicyclo[2.2.1]hepta-2,5-diene-2-carboxylate (HN) is irradiated at 290 nm with CPL, a one-way photocyclization

reaction proceeds to give methyl tetracyclo[3.2.0^{2.7}.0^{4.6}]heptane-1-carboxylate (HQ).

Theoretically, the relationship between the optical purity (%op) of the starting material and conversion (% conversion) is represented by equation (2).

$$\begin{aligned} x = 1 - (r + s) &= 1 - \left(\frac{1+y}{1-y} \right)^{\frac{1}{g}} \frac{1}{(1-y^2)^{1/2}} \\ &= 1 - \frac{1}{2} \left\{ \left(\frac{1+y}{1-y} \right)^{\frac{1}{g}+\frac{1}{2}} + \left(\frac{1+y}{1-y} \right)^{\frac{1}{g}-\frac{1}{2}} \right\} \end{aligned} \quad (2)$$

in which x is conversion (% conversion); y is the optical purity (%op) or %ee of the starting material; and g is the anisotropic factor of the starting material. Although equation (2) was presented by Kagan for analysis of an asymmetric photolysis process (*Tetrahedron Lett.* 1971, 2478-82), this equation can be applied to the starting material in class (A) in the absolute asymmetric synthesis method of the present invention.

The relationship between the optical purity (%op) or %ee of the product (y') and conversion (% conversion) (x) is defined by equations (3) and (4), in which R' and S' represent the products obtained from enantiomers R and S in the starting material.

$$\begin{aligned} y' &= \frac{([R'] - [S'])}{([R'] + [S'])} = \frac{([R]_0 - [R]) - ([S]_0 - [S])}{([R]_0 - [R]) + ([S]_0 - [S])} \\ &= \frac{-([R] - [S])}{([R]_0 + [S]_0) - ([R] + [S])} = \frac{-\{([R] - [S])/([R] + [S])\}}{\{([R]_0 + [S]_0)/([R] + [S])\} - 1} \quad (3) \end{aligned}$$

$$y' = \frac{y(1-x)}{x} \quad (4)$$

Fig. 1 (a) shows the relationship between the optical purity (%op) of the starting material (y) and conversion (x), calculated from equation (2) with different values of g .

The results show that the optical purity (%op) of the starting material (y) reaches nearly 100% at the final stage of the reaction for all values of g except for $g = 0$, i.e., no selective excitation with right- and left-circularly polarized light. Thus, when HN is irradiated at 290 nm with r - or l -CPL, (+)-HN or (-)-HN with an optical purity of nearly 100% can be obtained just before the end of the reaction.

Fig. 1 (b) shows the relationship between the optical purity (%op) of the product (y') and conversion (x), calculated from equations (2), (3) and (4) with different values of g . Fig. 1 (b) shows that at the initial stage of reaction, the optical purity (%op) of the

product reaches nearly $(g/2) \times 100\%$.

Fig. 1 show that, for example, when $g = 1$ and conversion is about 50%, the optical purities (%op) of the starting material and the product are both more than 40%.

5 According to the second embodiment of the invention, absolute asymmetric synthesis is realized by controlling the g in the above-mentioned reaction system. Of course, the kind of light and its wavelength are selected to provide a photochemically reversible reaction
10 system (class A).

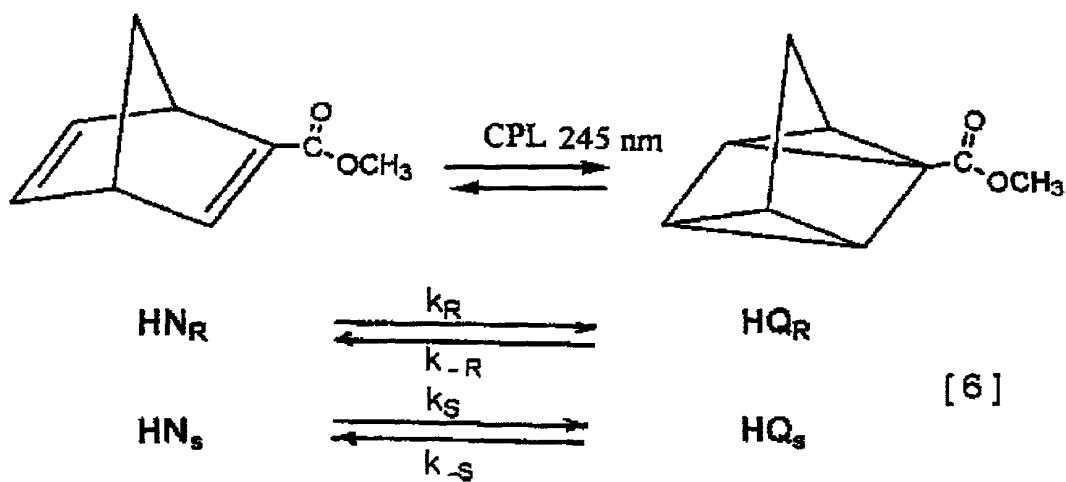
Class (B)

In class (B), as described in the third embodiment of the invention, the starting material and the product are mixtures of enantiomers, respectively and both
15 the starting material and the product are excited. One of the enantiomers in the starting material and one of the enantiomers in the product are concentrated by controlling at least one of the following:

20 g' s of the starting material and the product;
signs of the g' s; and
 K indicating the photochemical equilibrium of the reaction.

The starting material and the product are photochemically reversible, and both the forward reaction
25 and the reverse reaction can be carried out by irradiation

with light. Reaction scheme [6] shows a reversible reaction in which methyl bicyclo[2.2.1]hepta-2,5-diene-2-carboxylate (**HN**) is photocyclized to methyl tetracyclo[3.2.0^{2.7}.O^{4.6}]heptane-1-carboxylate (**HQ**) by 5 irradiation at 245 nm with CPL.



The rate equation of the photochemical reaction in this system is represented by the following:

$$\frac{dC}{dt} = -I_{ex} \left(1 - 10^{-\text{Abs}} \right) \frac{\varepsilon C}{\text{Abs}} \quad (6)$$

10

in which C is the concentration of the reactive component; I_{ex} is the intensity of absorption light ($I_0 - I$); Abs is the absorbance of the sample; ε is the molar absorption coefficient of the sample; Φ is the reaction yield; and t 15 is the reaction time. When $\text{Abs} > 1$, equation (6) can be

simplified to equation (7).

$$\frac{dC}{dt} = -I_{ex} \frac{\epsilon C}{Abs} \phi \quad (7)$$

When Abs is fairly constant during the reaction, the
5 factors other than C do not depend on t. Therefore,
equation (6) can be simplified to equation (8).

$$\frac{dC}{dt} = kC \quad (8)$$

In Reaction Scheme [6], enantiomers of HQ (HQ_R and HQ_S) are converted into HN (HN_R and HN_S) by CPL
irradiation, respectively. Abs in equations (6) and (7)
10 is represented by the following:

$$Abs = d(\epsilon_{QR}C_{QR} + \epsilon_{QS}C_{QS} + \epsilon_{NR}C_{NR} + \epsilon_{NS}C_{NS}) \quad (9)$$

in which d is the optical path length and C is the
concentration of each component. According to the law of
conservation of mass, the following relationships exist
15 between various concentrations (C):

$$C_O = C_Q + C_N = C_{QR} + C_{QS} + C_{NR} + C_{NS} \quad (10)$$

and

$$C_O/2 = C_{QR} + C_{NR} = C_{QS} + C_{NS} \quad (11)$$

When the ϵ values of R-isomer and S-isomer are almost
20 equal to each other (i.e., the g is small), Abs is
represented by the following:

$$\text{Abs} = d\{\varepsilon_N C_0 + (\varepsilon_Q - \varepsilon_N) C_Q\} \quad (12)$$

In this case,

$$\varepsilon_Q = 1/2(\varepsilon_{QR} + \varepsilon_{QS}) \text{ and } \varepsilon_N = 1/2(\varepsilon_{NR} + \varepsilon_{NS}) \quad (13)$$

The rate equations of HQ_R and HQ_S in Reaction Scheme [6] are represented by the following:

$$\frac{dC_{QR}}{dt} = -k_R C_{QR} + k_{-R} C_{NR} \quad (14)$$

$$\frac{dC_{QS}}{dt} = -k_S C_{QS} + k_{-S} C_{NS}$$

Therefore, the optical purities (%op) of HQ and HN , and conversion (x) are defined as follows:

10

$$\text{op}_Q = \frac{C_{QR} - C_{QS}}{C_{QR} + C_{QS}} \quad (15)$$

$$\text{op}_N = \frac{C_{NR} - C_{NS}}{C_{NR} + C_{NS}} = -\text{op}_Q \frac{1-x}{x} \quad (16)$$

$$x = \frac{C_N}{C_0} = \frac{C_{NR} + C_{NS}}{C_0} = \frac{C_0 - (C_{QR} + C_{QS})}{C_0} \quad (17)$$

The molar absorption coefficient of R -isomer (QR) generated by 1-CPL irradiation of HQ is equal to that

of *S*-isomer (*QS*) generated by *r*-CPL irradiation of HQ.

Therefore, g_Q can be rewritten as follows:

$$g_Q = 2 \frac{\epsilon'_{QR} - \epsilon'_{QS}}{\epsilon'_{QR} + \epsilon'_{QS}} = 2 \frac{\epsilon'_{QR} - \epsilon'_{QS}}{\epsilon'_{QR} + \epsilon'_{QS}} = 2 \frac{k_R - k_S}{k_R + k_S} \quad (18)$$

The progress of the reaction expressed by equation (14) exhibits the following relationships, using 5 parameters such as g_Q , g_N , K , L and M :

$$\frac{C_{QR}}{C_0} = \frac{1}{2} \frac{K}{K+1} + \frac{1}{2} \frac{1}{K+1} e^{\left\{-k_R t \left(1 + \frac{1}{K}\right)\right\}} \quad (19)$$

$$\frac{C_{QS}}{C_0} = \frac{1}{2} \frac{M}{KL+M} + \frac{1}{2} \frac{KL}{KL+M} e^{\left\{-k_R t \left(L + \frac{M}{K}\right)\right\}} \quad (20)$$

K , L and M are defined as follows:

$$K = \frac{k_R + k_S}{k_R + k_S} \quad (21)$$

$$L = \frac{k_S}{k_R} = \frac{1 - \frac{g_Q}{2}}{1 + \frac{g_Q}{2}} \quad (22)$$

$$M = \frac{k_S}{k_R} = \frac{1 - \frac{g_N}{2}}{1 + \frac{g_N}{2}} \quad (23)$$

Thus the optical purities (%op) of HQ and HN, and conversion (x) can be represented by the following:

$$op_Q = \frac{(K^2L + K - MK - L) + (KL + 1)e^{-k_R t} \left(1 + \frac{1}{K}\right)}{(K^2L + K + MK + L) + (KL + 1)e^{-k_R t} \left(1 + \frac{1}{K}\right)} e^{-k_R t \left(L + \frac{M}{K}\right)} \quad (24)$$

$$op_N = -op_Q \frac{1-x}{x} \quad (25)$$

$$x = 1 - \left[\frac{1}{2} \frac{K}{K+1} + \frac{1}{2} \frac{1}{K+1} e^{-k_R t \left(1 + \frac{1}{K}\right)} + \frac{1}{2} \frac{M}{KL+1} + \frac{1}{2} \frac{KL}{KL+1} e^{-k_R t \left(L + \frac{M}{K}\right)} \right] \quad (26)$$

5

From the above, it is clear that absolute asymmetric synthesis can be realized in class (B) by adjusting the following:

- g 's of the starting material and the product;
- 10 • signs of the g 's for the starting material and the product;
- photochemical equilibrium (K) between the starting material and the product,

thereby controlling the optical purities (%op) of the

15 starting material and the product, and conversion (x).

Fig. 2 illustrates the relationship among the g ,

the sign of g and optical purity (%op).

Fig. 2 shows the optical purities (%op) of **HQ** and **HN**, calculated from equations (24), (25) and (26) with various values of g_Q and g_N . The following two cases (I) 5 and (II) are shown therein:

(I) $g_Q \cdot g_N > 0$; ($g_Q = 1.0, g_N = 1.0$: solid line) or ($g_Q = -1.0, g_N = -1.0$: broken line), $K = 0.072$.

(II) $g_Q \cdot g_N < 0$; ($g_Q = 1.0, g_N = -1.0$: broken line) or ($g_Q = -1.0, g_N = 1.0$: solid line), $K = 0.072$.

10 Case (I) shows $k_R > k_S$ and $k_{-R} > k_{-S}$, and case (II) $k_R > k_S$ and $k_{-R} < k_{-S}$, as obtained from equation (18).

Fig. 2 (a) shows the following results:

In case (I), the optical purity (%op) of the starting material (**HQ**) gradually increases at the beginning of 15 conversion but decreases in the course of the reaction.

In the photostationary state (pss), the optical purity (%op) reaches zero. In case (II), the optical purity (%op) of the starting material (**HQ**) increases with the conversion and reaches a maximum in the photostationary 20 state (pss).

Fig. 2 (b) shows the following results:

In case (I), the optical purity (%op) of the starting material (**HN**) decreases from the beginning of the reaction and reaches zero in the photostationary state (pss). In 25 case (II), the optical purity (%op) of the starting

material (**HN**) increases as the reaction progresses, and reaches a maximum in the photostationary state (pss).

In case (II), the optical purities (%op) of the starting material (**HQ**) and the product (**HN**) increase as 5 the reaction progresses. That is, generally, when the signs of the g 's of the starting material and the product are different from each other, the optical purities (%op) of the starting material and the product increase.

In the absolute asymmetric synthesis of the 10 present invention, sameness or difference of the signs of the g 's of the starting material and the product at a CPL irradiation wave length has a large effect on the relationship between the conversion and optical purities (%op) of the starting material and the product.

15 Fig. 3 shows the relationship between the optical purity (%op) and K value.

Fig. 3 shows the results obtained from equations (24), (25) and (26), in the case of $g_Q \cdot g_N < 0$, $g_Q = -1.0$ and $g_N = 1.0$ and the case of $g_Q = 1.0$ and $g_N = -1.0$.

20 The following results are indicated. The optical purity (%op) of the starting material (**HQ**) increases as the reaction progresses. Especially, as K is smaller, the optical purity (%op) increases more sharply.

The optical purity (%op) of the product (**HN**) 25 increases when K is less than 1. As K becomes larger, the

optical purity (%op) gradually decreases. When $K=\infty$, the optical purity (%op) of the product becomes zero at the end of the reaction. The relationship is the same as in the irreversible reaction.

- 5 The above results reveal the following:
when K is less than 1, the optical purity of the product increases as the conversion is increased. In class (A),
the optical purity (%op) of the product does not increase beyond the value achieved at the initial stage of reaction,
10 i.e., $(g/2) \times 100\%$. In contrast, the optical purity (%op) obtained by the reaction in class (B) increases far beyond this value.

As described above, the first embodiment of the invention enables concentration of one starting material
15 enantiomer or diastereomer and one product enantiomer or diastereomer (or achieving further concentration of one starting material enantiomer or diastereomer and one product enantiomer or diastereomer, if already concentrated). According to the second embodiment of the invention, in a reaction system of class (A), one starting material enantiomer and one product enantiomer are concentrated by controlling the g of the starting material.
According to the third embodiment of the invention, in a reaction system of class (B), one starting material
25 enantiomer and one product enantiomer are concentrated by

controlling at least one of the following:

g's of the starting material and product;

signs of the *g*'s; and

K indicating the photochemical equilibrium of the

5 reaction.

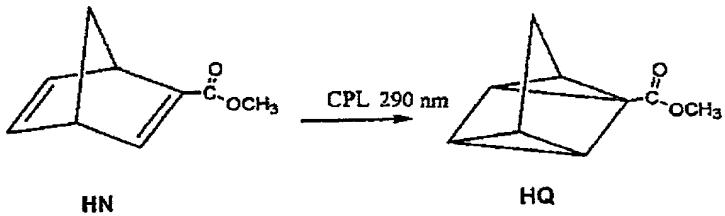
The present invention will be described below in further detail with reference to Examples.

EXAMPLES

10 (Example 1)

Absolute asymmetric synthesis was conducted in the reaction system which contains methyl bicyclo[2.2.1]hepta-2,5-diene-2-carboxylate (**HN**) represented by the formula below and methyl tetracyclo[3.2.0.0^{2,7}.0^{4,6}]heptane-1-carboxylate (**HQ**) .

15



<1> Optical properties of **HN** and **HQ**

HN and **HQ** were measured for their UV spectra and CD spectra (in CH₃CN). The results are shown in Fig. 4 together with the *g* values derived from these spectra.

20 The specific rotations (in CH₃CN) were

(-) - **HN**: [α]²⁰_D = -41.5 (c=0.0624)

(+)-HQ: $[\alpha]^{20}_D = 322$ ($c=0.00375$)

Although norbornadiene and methyl acrylate regarded as model compounds of **HN** do not have any absorption bands at wavelengths longer than about 250 nm, as is apparent from Fig. 4 (a), the UV spectrum of (\pm) -**HN** exhibits two absorption maxima at about 229.5 and 265 nm. As shown in Fig. 4 (c), (+)-**HN** and (-)-**HN** give the CD spectra from 200 to 340 nm. Fig. 4 (e) indicates that anisotropic factor g of (+)-**HN** and (-)-**HN** also exhibit two maxima in this region.

The foregoing shows that broad absorption of this region consists of two bands.

On the contrary, as shown in Fig. 4 (b), the UV spectrum of (\pm) -HQ exhibit one absorption band composed of an absorption maximum at about 215 nm and an absorption declining toward about 250 nm. This absorption band corresponds to that of methyl acrylate which does not exhibit any absorption at wavelengths longer than 250 nm. As shown in Fig. 4 (d), the CD spectra of (+)-HQ and (-)-HQ have the maximum at about 215 nm, and thus absorption bands in the UV and CD spectra appear to be composed of a single band. However, the two maxima of anisotropic factor g at 217.5 and 263.5 nm indicate that the UV and CD spectra of (+)-HQ and (-)-HQ actually is composed of two

bands.

<2> Efficiency of photocyclization and stereochemistry

The efficiency and stereochemical aspect of the photocyclization of **HN** into **HQ** were evaluated by
5 irradiating (-)-**HN** with a linearly polarized light (LPL) at a wavelength of 290 nm, which is not absorbed by **HQ**.

Fig. 5 (a) shows changes in UV spectra of (-)-**HN** in CH_3CN (0.236 mM) irradiated at 290 nm with light. This figure shows spectra at various irradiation times (0, 31,
10 60 and 127 minutes) and the spectrum of (+)-**HQ**. The absorption bands of (-)-**HN** at 228 and 256 nm gradually disappeared, and a new absorption band resembling the UV spectrum of **HQ** appeared at about 220 nm. Two isosbestic points were found at 209 and 218 nm by the
15 photoirradiation.

The reaction mixture was analyzed by gas chromatography using biphenyl as an internal standard. UV spectrum and gas chromatography revealed that the total concentration of **HN** and **HQ** was retained after CPL
20 irradiation and no by-products were present.

These results indicate that the photocyclization progressed quantitatively and no side reactions occur. The fact that the spectrum of (-)-**HN** irradiated for 127 minutes closely agrees with that of **HQ** confirmed that the
25 photoirradiation efficiently causes the one-way

isomerization from **HN** into **HQ**.

Fig. 5 (b) shows changes in CD spectra when (-)-**HN** was irradiated with 290 nm light. This figure shows the spectra at various irradiation times (0, 31, 60 and 127 min.) and spectrum of (+)-**HQ**. The absorption maxima of (-)-**HN** at 229 and 271.5 nm gradually decreased, and a new absorption maximum appeared at about 215 nm. An isosbestic point was observed at 207 nm.

The changes in UV and CD spectra as mentioned above were measured at a wavelength of 290 nm where the product cannot absorb excitation light. The results of the measurement revealed that there was no influence of side reactions or the like. The spectrum of (-)-**HN** irradiated for 127 minutes corresponds to that of (+)-**HQ** having the same concentration. This fact confirmed that (-)-**HN** is isomerized into (+)-**HQ** without racemization.

<3> Absolute asymmetric synthesis with CPL

Absolute asymmetric synthesis was carried out by CPL-irradiating (\pm)-**HN** at 290 nm.

Fig. 6 shows changes in UV spectrum over time irradiated at 290 nm with *r*-CPL.

The intensity of the absorption bands decreased at about 270 nm, and the UV spectrum showed two isosbestic points at 209 and 218 nm. A similar change in the UV spectrum was observed when **HN** was irradiated at 290 nm

with *l*-CPL or LPL.

Fig. 7 shows the relationship between the irradiation time of (\pm)-HN and conversion when irradiated at 290nm with *r*- and *l*-CPL and LPL. In this figure, white dots represent *l*-CPL irradiation; black dots represent *r*-CPL irradiation; and white triangles represent LPL irradiation. Because the plots are overlapping, it is considered that the intensities of the right and left-handed CPL and LPL as incident light are almost equal.

Fig. 8 (a) shows changes in CD spectra of HN (acetonitrile solution) when irradiated at 290 nm with *l*- and *r*-CPL. The figure indicates that the intensities of the two peaks at about 220 and 280 nm are increasing over time during irradiation.

Fig. 8 (b) shows the calculated values of the CD spectra of irradiated (\pm)-HN. It is assumed from this figure that (-)-HN is selectively excited with *r*-CPL (290 nm) and the concentration of (+)-HN increases.

It is well known that photocyclization is a unimolecular reaction. Thus, a decrease in HN concentration equals to an increase in HQ concentration. When a solution of HN is irradiated at 290 nm with *r*-CPL, the CD spectrum appears as a 1:1 mix of the CD spectrum of (+)-HN and $\Delta\epsilon$ spectrum of (+)-HQ.

The spectrum shown in Fig. 8 (b) was calculated

based on the above view. It was confirmed that the spectrum of Fig. 8 (a) obtained experimentally precisely agreed with the calculated spectrum of Fig. 8 (b).

The CD absorption band at about 280 nm shown in
5 Fig. 8 (a) reflects the concentration of one of enantiomers of **HN**. The value of $\Delta\epsilon$ of (\pm) -**HQ** at 280 nm is 0. Thus the optical purity of **HN** can be determined from the value of ellipticity (θ) at 280 nm. The absorption band at about 220 nm reflects the concentration of one of
10 enantiomers of **HQ**. In particular, because the value of $\Delta\epsilon$ of (\pm) -**HN** at 245 nm is 0, the optical purity of **HQ** can be determined using the value of Q at this wavelength.

Fig. 9 (a) shows the relationship between the conversion and the optical purity (%op) of **HN** calculated
15 from the concentration determined by the measurement of CD and UV spectra.

Fig. 9 (b) shows the relationship between the optical purity (%op) of **HQ** and the conversion. In Figs. 9
20 (a) and (b), black dots represent the results of *r*-CPL irradiation and white dots represent the results of *l*-CPL irradiation.

Fig. 9 (a) indicates that the optical purity (%op) of **HN** increases as the conversion ratio increases.

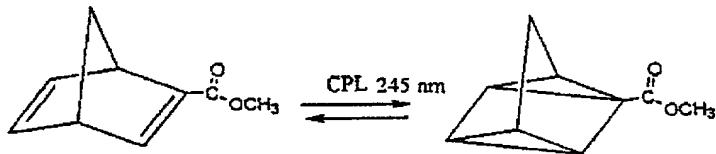
The solid lines in Figs. 9 (a) and (b) are
25 theoretically depicted with Kagan's equation (equation (2)

described above) using the measurement of g value ($g=0.012$) at 290 nm. The curves of solid lines show good agreement with the experimental data.

Therefore, it was confirmed that (\pm) -HN
5 irradiated with r - and l -CPL at 290 nm increased concentrations of $(+)$ -HN and $(-)$ -HN, and the behavior of $\%op$ agreed with equation (2) described above.

(Example 2)

Absolute asymmetric synthesis was carried out as
10 a photochemical reaction represented by the following formula.



As shown in Figs. 4 (e) and (f) mentioned above, when HQ is irradiated at 245 nm with CPL, one of the 15 enantiomers is selectively excited. However, the g 's of $(+)$ -HN and $(-)$ -HN at 245 nm are 0. This means that the selection is not effective in excitation of HN.

Therefore, irradiation of HQ with CPL at the wavelength of 245 nm is discussed.

20 Fig. 10 shows the measurements of changes in UV spectra of HQ solution irradiated at 245 nm with l -CPL. The absorption intensity was increased at about 270 nm by l -CPL photoirradiation at 245 nm, and the UV spectra show

two isosbestic points at 208 nm and 212 nm.

Similar changes in UV spectrum of the HQ solution were observed when irradiated at 245 nm with *r*-CPL or LPL.

The solution was analyzed by gas chromatography 5 using biphenyl as an internal standard. The gas chromatography chart did not show any signals other than HQ and HN, confirming that the total amount of HQ and HN is maintained.

The appearance of the two isosbestic points of UV 10 spectra and the results of gas chromatography analysis of the solution indicate that HQ is photochemically isomerized into HN without any side reactions. Thus, since HQ is isomerized into HN by photoirradiation at 245 nm, the conversion of HQ into HN is measured by the 15 intensity of UV absorption at 280 nm, which reflects the concentration of the product HN.

Fig. 11 shows the measurements of changes in CD spectra of HQ solution irradiated with *l*-CPL or *r*-CPL at 245 nm.

20 Two absorption maxima are observed at about 215 nm and 270 nm, and their intensities increase over time due to CPL photoirradiation.

Fig. 12 shows calculation results of CD spectra of HQ solution irradiated at 245 nm with *r*-CPL. When the 25 HQ solution is irradiated at 245 nm with *r*-CPL, (-)-HQ is

preferentially excited, whereby (+)-HQ remains and (+)-HN is isomerized into (-)-HQ. Therefore, (-)-HQ excited with *r*-CPL is isomerized into (+)-HN. This isomerization does not cause any side reactions. In addition,

- 5 photoisomerization is known to be a unimolecular reaction. Therefore, the CD spectra of the HQ solution when irradiated at 245 nm with *r*-CPL is composed of the CD spectrum of (+)-HQ and CD spectrum of (+)-HN, and their composition ratio of 1:1 at the initial stage. After
10 continuing photoisomerization, the value of ϵ of HN is higher than that of HQ at about 245 nm and HN start to be excited by CPL irradiation. Therefore, CD absorption at about 215 nm is higher than that at about 270 nm. In either case, the actual CD spectrum of the HQ solution
15 irradiated at 245 nm with *r*-CPL is assumed to be similar to the thicker solid line in Fig. 12.

When the HQ solution is irradiated at 245 nm with *l*-CPL in the same manner, its CD spectra is composed of the CD spectrum of (-)-HQ and CD spectrum of (-)-HN and
20 the calculated shape of CD spectra resemble that shown in Fig. 12.

Accordingly, the above simulation shows that the change at about 280 nm in CD spectrum during the isomerization of HQ irradiated with 245 nm CPL reflects a
25 change in HN concentration, and the change at about 220 nm

reflects a change in **HN** concentration caused by the isomerization of **HQ** irradiated at 245 nm with CPL.

Since $(+)$ -**HQ** and $(-)$ -**HQ** do not have any CD absorption at 280 nm, the optical purities of $(+)$ -**HN** and 5 $(-)$ -**HN** are determined by the ellipticities (θ) at 280 nm. Because $\Delta\epsilon$ of $(+)$ -**HN** and $(-)$ -**HN** are 0 at 245 nm, the optical purities of $(+)$ -**HQ** and $(-)$ -**HQ** are determined by the ellipticities (θ) at 245 nm.

Therefore, **HQ** solution is irradiated with 245 nm 10 CPL to cause absolute asymmetric synthesis. Fig. 13 shows the relationship between the optical purity (%op) and conversion ratio which is obtained as an experimental result. In this figure, the black dots represent the results of *r*-CPL irradiation; the white dots represent the 15 results of *l*-CPL irradiation; and the solid line represents the value calculated by simulation in which $g_0 = \pm 0.0074$, $g_N = 0$ and $K = 0.667$.

As is apparent from Fig. 13, the results of experiment and simulation show good agreement. Thus, the 20 optical purity (%op) of **HQ** increases and the optical purity (%op) of **HN** decreases as conversion ratio increases. In the photostationary state, the optical purity (%op) of **HQ** reaches a maximum and the optical purity (%op) of **HN** becomes minimal.

25 Next, concerning reversible photoisomerization of

HN into HQ caused by 245 nm CPL irradiation, the relationship between the conversion ratio and the optical purities (%op) of the starting material and the product was analyzed.

5 Changes in the UV spectra of HN solution under irradiation of 245 nm CPL closely resembled those shown in Example 1. Photoirradiation with 245 nm CPL further weakened the absorption at about 270 nm, and the UV spectra exhibited two isosbestic points at about 208 nm
10 and about 212 nm.

These results indicate that no side reactions occur in this photoreaction. Thus, conversion ratio from HN into HQ was determined by the intensity of UV absorption at 280 nm.

15 Changes in CD spectra closely resembled those shown in Fig. 11. Therefore, the optical purities of (+)-HN and (-)-HN were determined by the ellipticities at 280 nm, and the optical purities of (+)-HQ and (-)-HQ were determined by the ellipticities at 245 nm.

20 Because the g of HN is 0 at 245 nm, enantiomers are not concentrated by CPL irradiation at the initial stage of photoisomerization from HN into HQ. However, CPL serves as an asymmetric source for HQ produced by photoisomerization of HN. As the conversion ratio from HN
25 into HQ increases, the produced HQ is excited by CPL and

the concentration of one enantiomer of HQ progresses.

Accordingly, the concentration of one enantiomer of HN also progresses.

Fig. 14 shows the relationship between the
5 optical purity (%op) and conversion ratio as experimental data (black dots: *r*-CPL irradiation, white dots: *l*-CPL irradiation) and simulated calculation results (solid line) of HN in acetonitrile irradiated at 245 nm with CPL. The simulated calculation results are when $g_N = 0$, $g_0 = \pm 0.0074$ and $K=1.5$. The experimental results and
10 calculated results showed good agreement. The optical purities (%op) of HN and HQ increase as conversion ratio increases. In the photostationary state, the values of these optical purities (%op) were almost equal.

15 The above results show that the aforementioned reaction system of class (B) in absolute asymmetric synthesis is formed.

Further, the results of theoretical and experimental analyses reveal the following: the
20 concentration of one of the enantiomers in the starting material and one of the enantiomers in the product can be controlled by adjusting the g 's of both starting material and product, the plus or minus sign of the g 's and the K , which represent photochemical equilibrium of the reaction;
25 the optical purities (%op) of the starting

material and product increase as the conversion ratio increases when the g 's of the starting material and product are sufficiently high, the signs of the g of the starting material is opposite to that of the product, and

5 K is not 1;

and the optical purities of the starting material and product increase to a considerable extent in the photostationary state. This indicates that Kagan's assumption that the purity of enantiomers of the product
10 decreases by the process of photoreaction is not always the case in the absolute asymmetric synthesis of class (B). The above Examples reveal that one of the enantiomers in the starting material and one of the enantiomers in the product can be concentrated by the progress of
15 photoreaction using CPL irradiation.

INDUSTRIAL APPLICABILITY

As described above in detail, the present invention provides a novel method for absolute asymmetric synthesis comprising irradiating the reaction system with circularly polarized light, the method enabling concentration of one of the enantiomers in the starting material and one of the enantiomers in the product.

-40-

CLAIMS

1. (Amended) A method for synthesizing absolute asymmetry which comprises:
 - 5 providing a photochemically reversible reaction system in which the starting material and the product are mixtures of enantiomers or diastereomers not photochemically or thermally converted into each other; and
 - 10 irradiating the reaction system with right- or left-circularly polarized light to excite the starting material alone or both of the starting material and the product, thereby concentrating one of the enantiomers or diastereomers in the starting material and one of the enantiomers or diastereomers in the product that
 - 15 corresponds to the enantiomer or diastereomer not concentrated in the starting material.
2. The method according to claim 1 wherein the starting material and the product are mixtures of enantiomers and only the starting material is excited, the concentration of one of the enantiomers in the starting material and one of the enantiomers in the product being controlled by adjusting the anisotropic factor g which indicates the degree of selective excitation by right- and left-circularly polarized light.

3. The method according to claim 1 wherein the starting material and the product are mixtures of enantiomers and both of the starting material and the product are excited, the concentration of one of the
5 enantiomers in the starting material and one of the enantiomers in the product being controlled by adjusting at least one of the following:

the value of anisotropic factor g which indicates the degree of selective excitation by right- and left-
10 circularly polarized light;
plus or minus sign of g ; and
 K indicating the photochemical equilibrium of the reaction.

SEARCHED.....INDEXED.....

Abstract

The present invention provides a novel method for absolute asymmetric synthesis by irradiation with 5 circularly polarized light, which comprises providing a photochemically reversible reaction system in which the starting material is a mixture of enantiomers or diastereomers not photochemically or thermally converted into each other; 10 and irradiating the reaction system with right- or left- circularly polarized light to excite the starting material alone or both of the starting material and the product, thereby concentrating one of the enantiomers or 15 diastereomers in the starting material and one of the enantiomers or diastereomers in the product that corresponds to the enantiomer or diastereomer not concentrated in the starting material.

Fig. 1

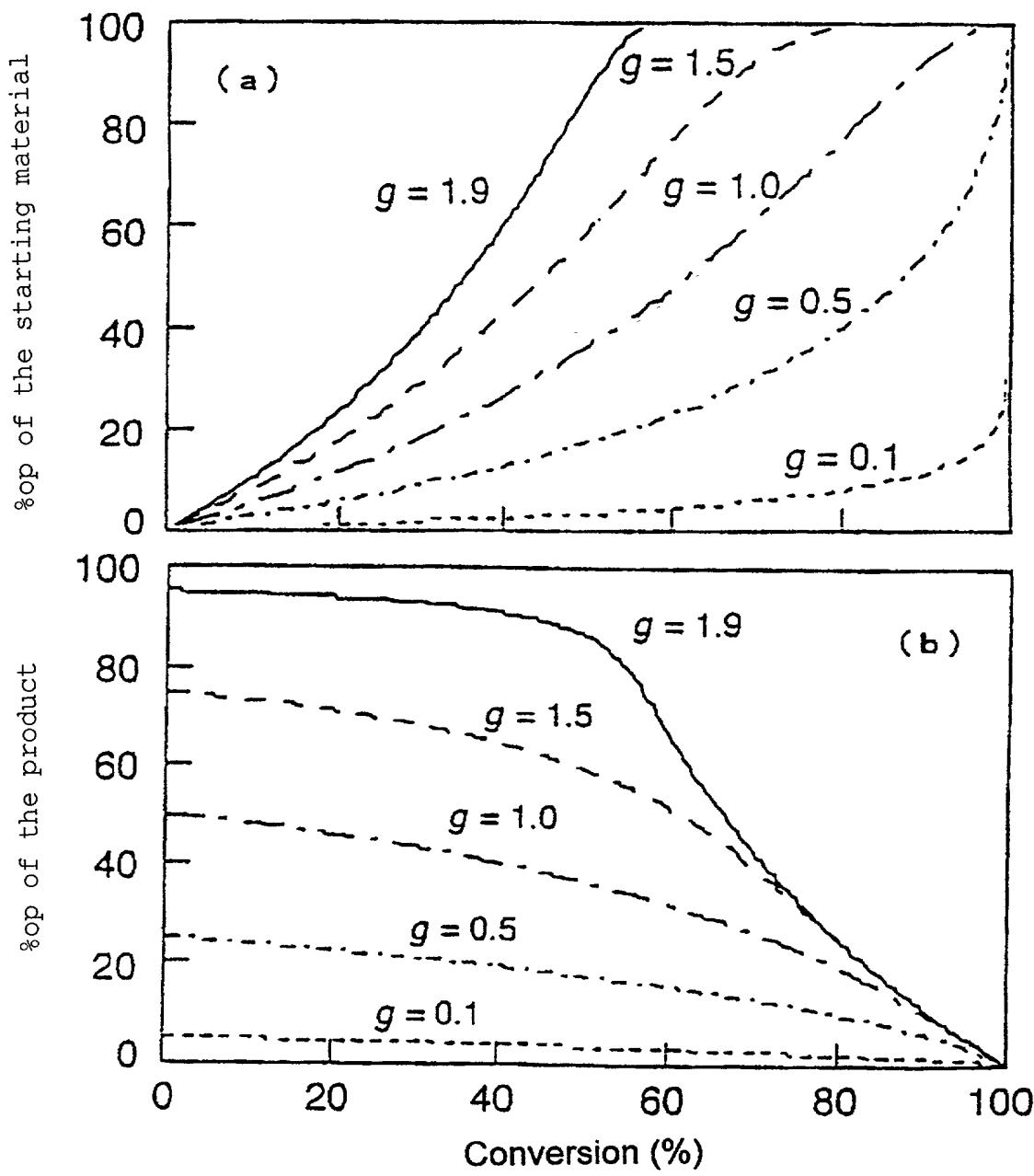


Fig. 2

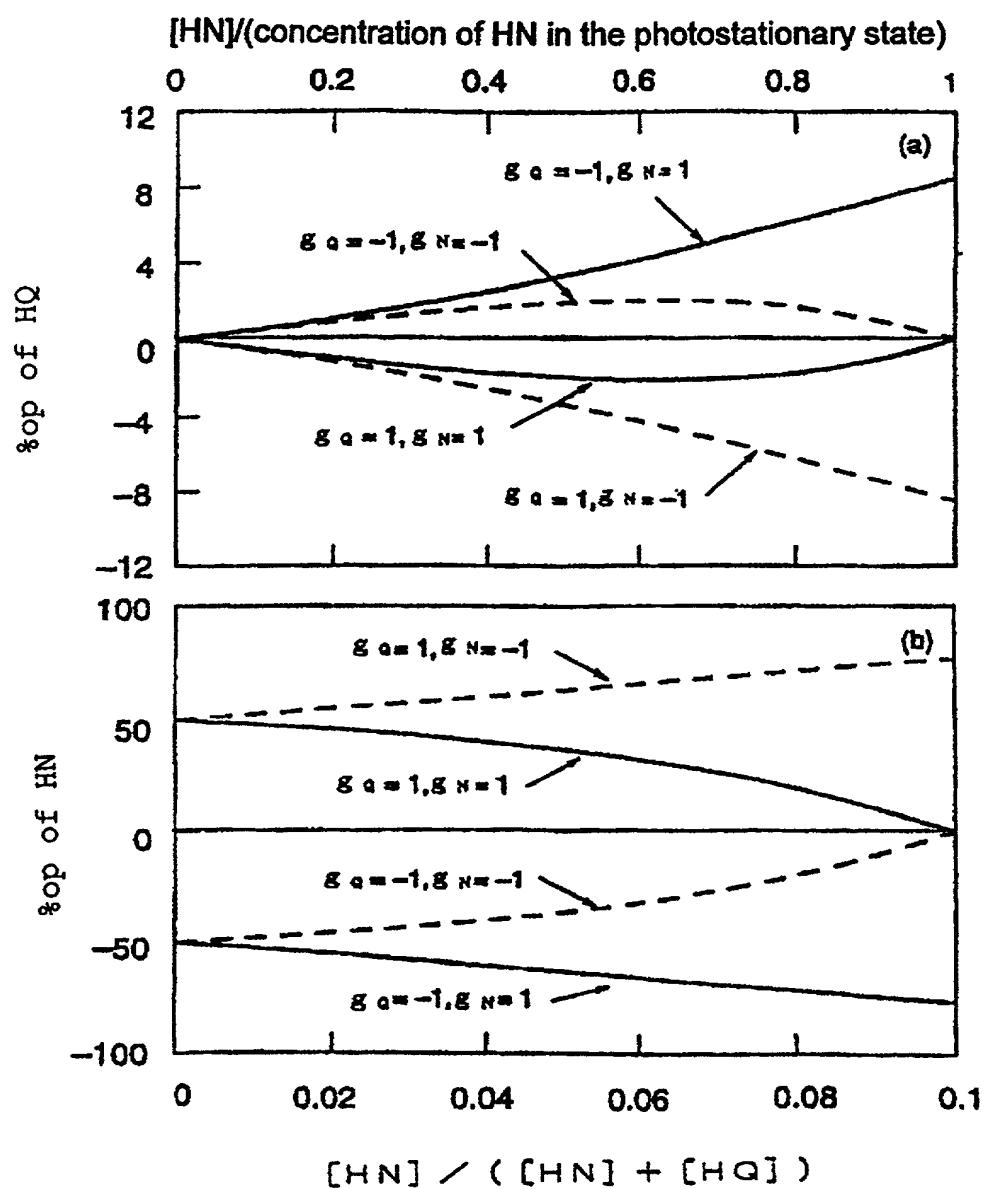


Fig. 3

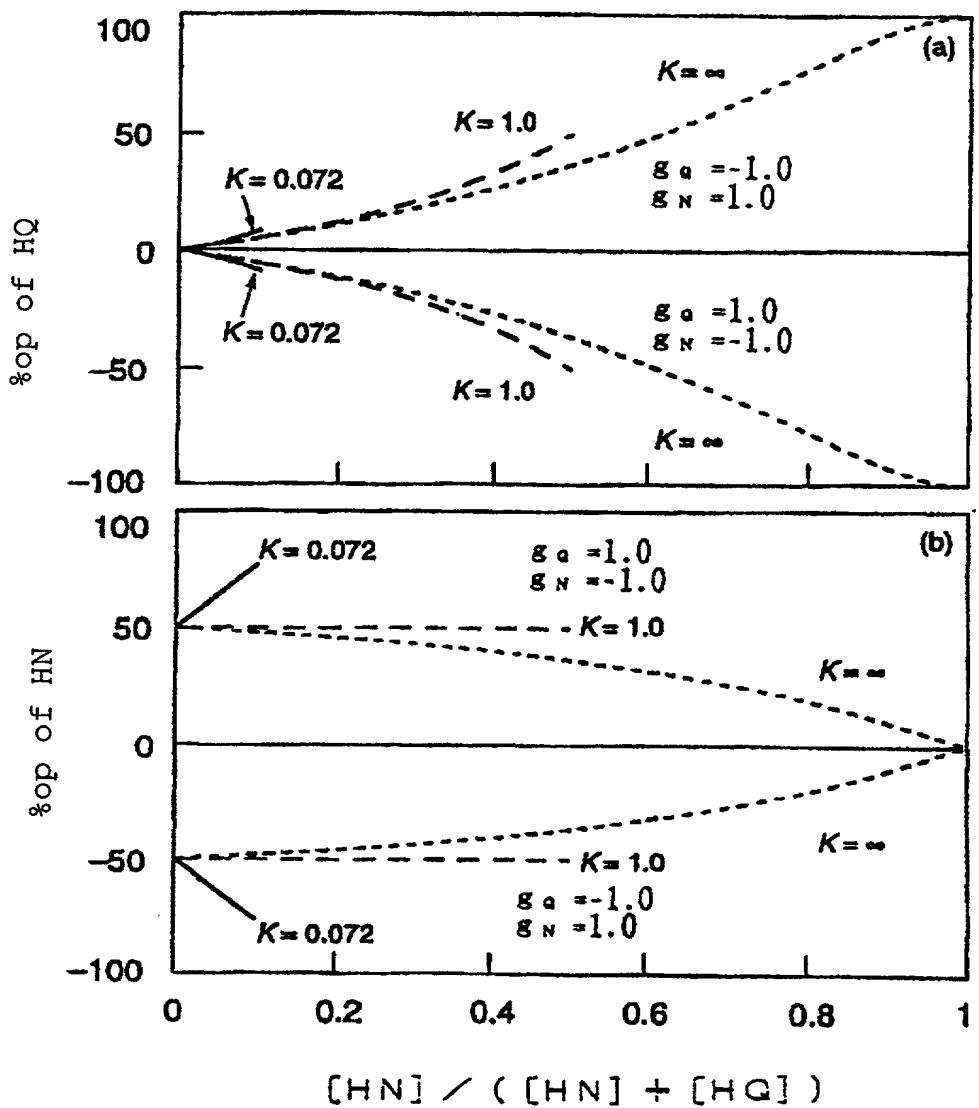


Fig. 4

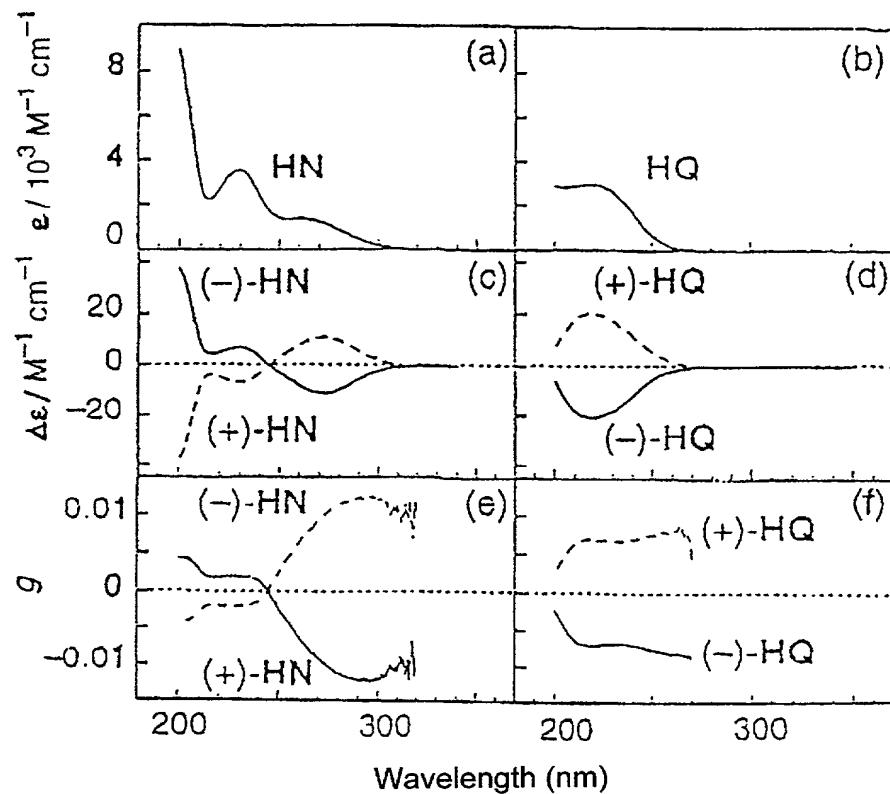


Fig. 5

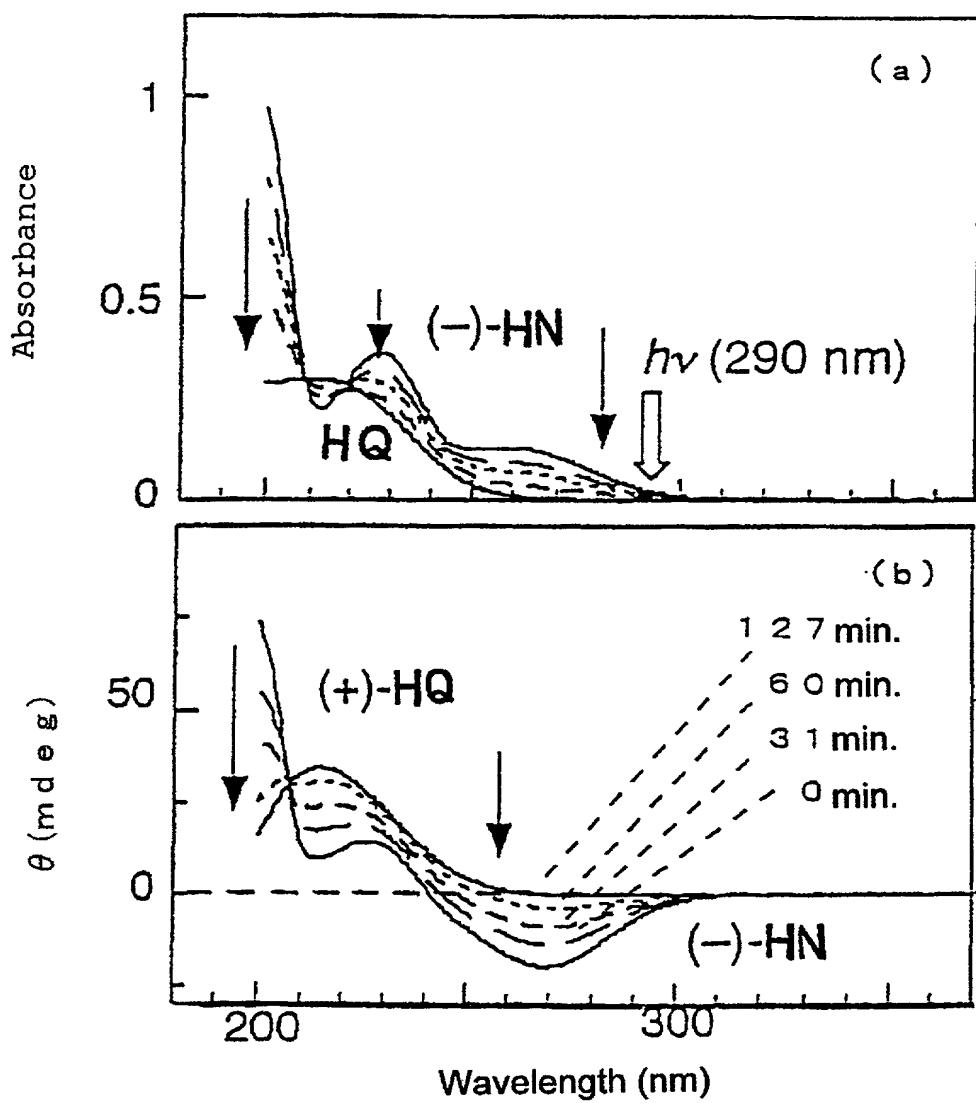


Fig. 6

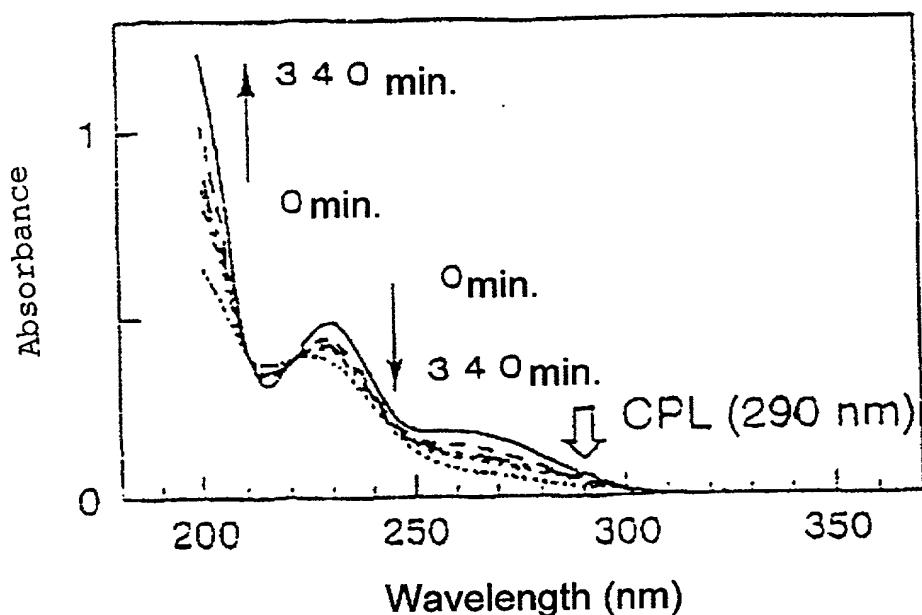


Fig. 7

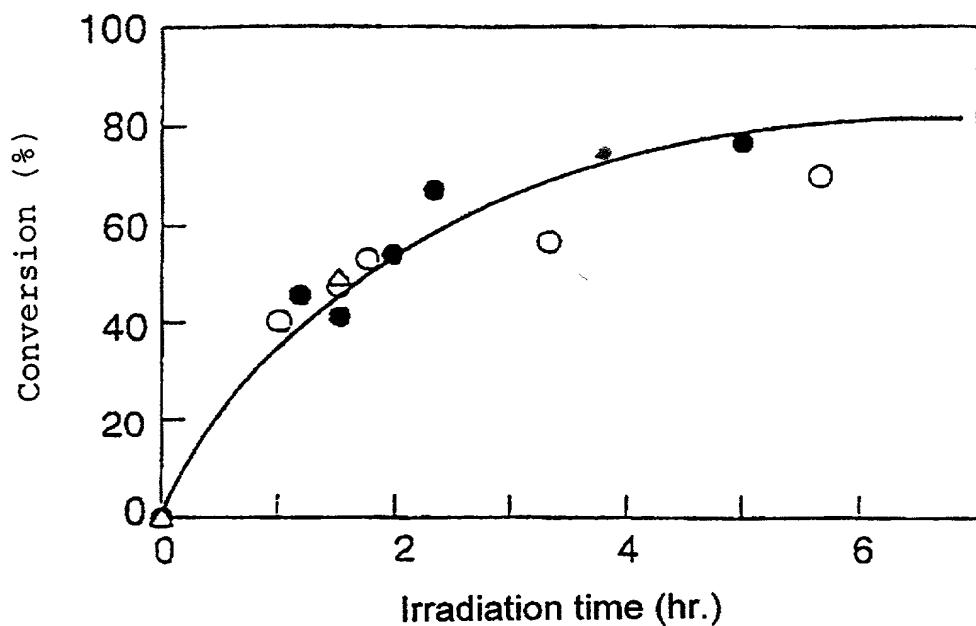


Fig. 8

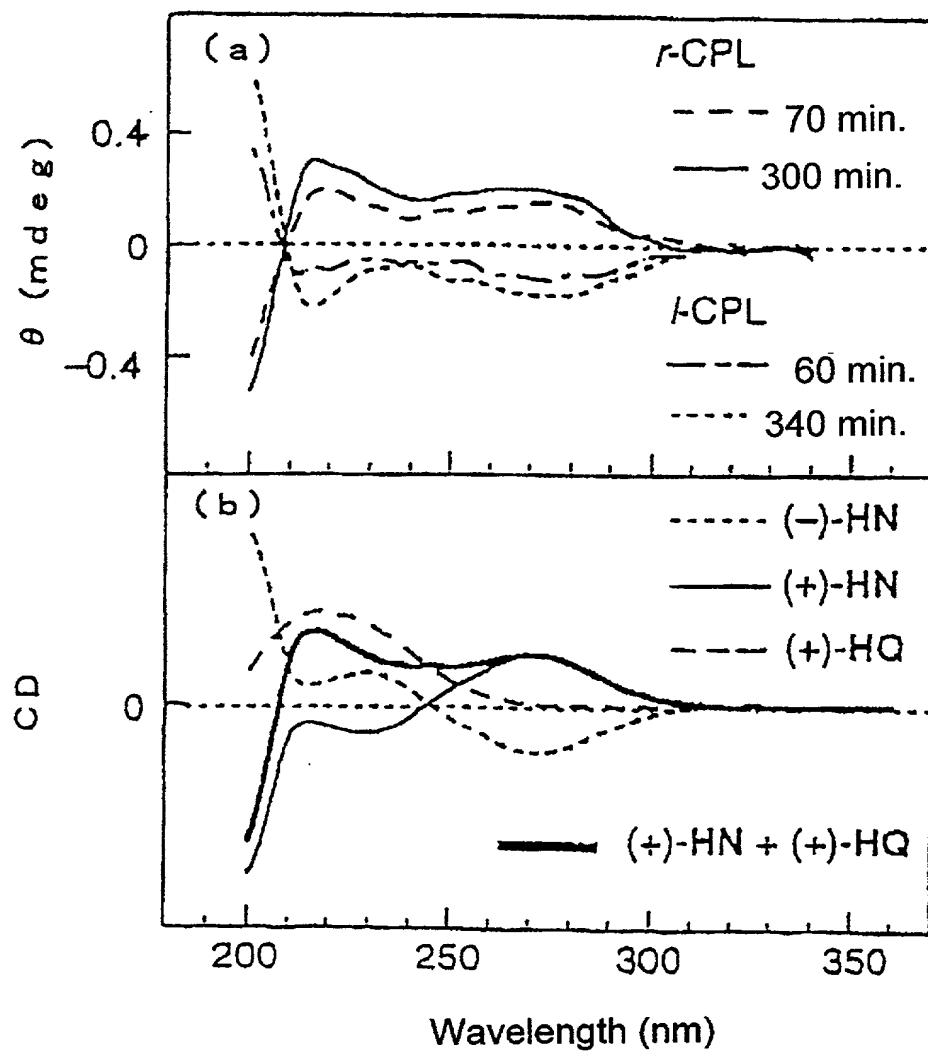
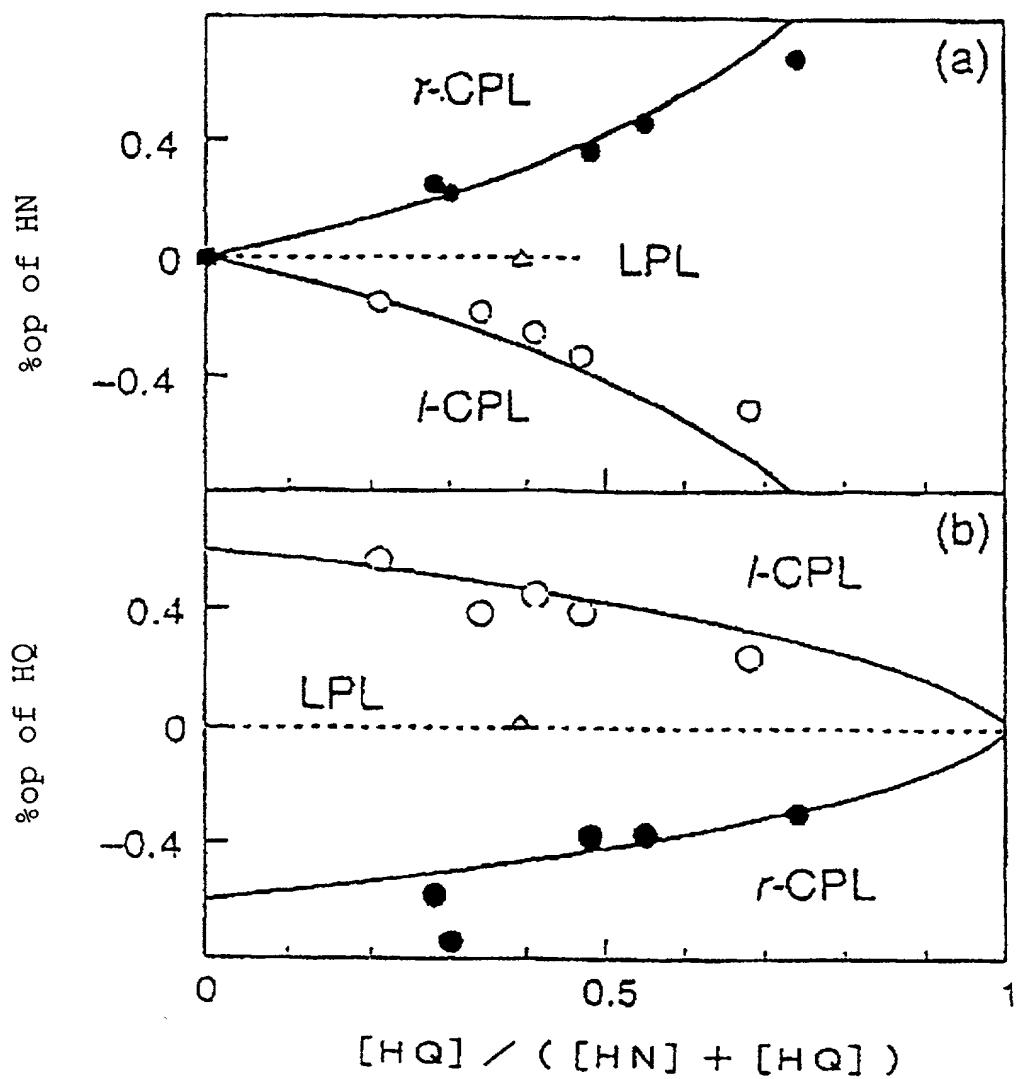


Fig. 9



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Fig. 10

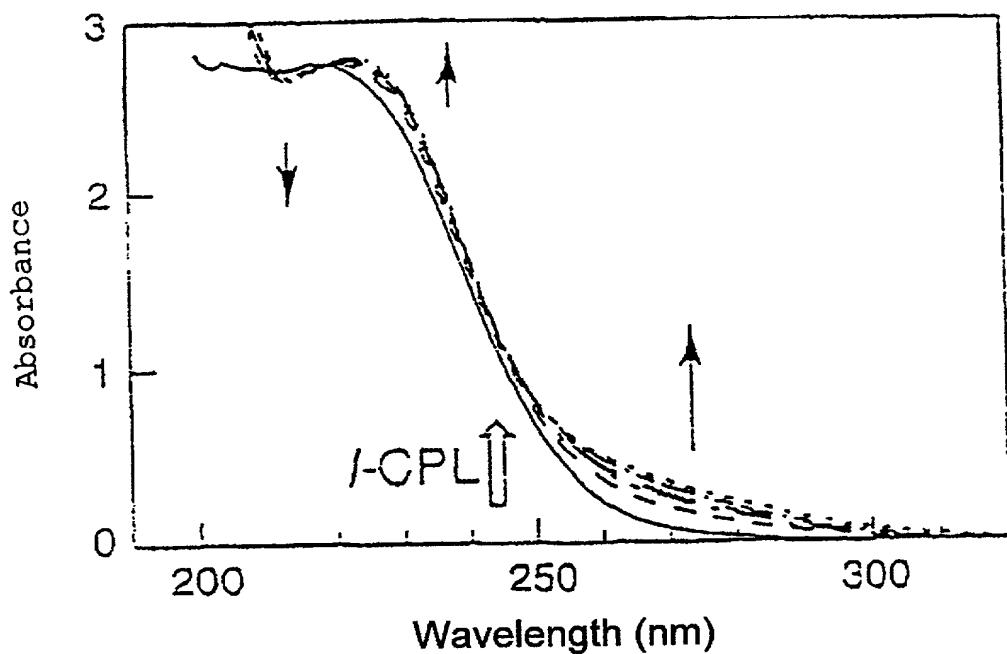


Fig. 11

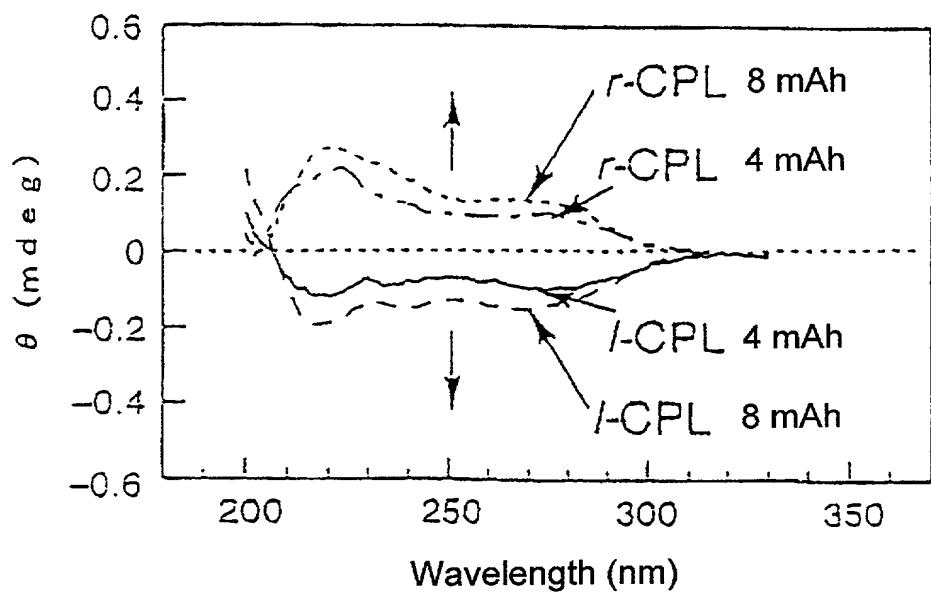


Fig. 12

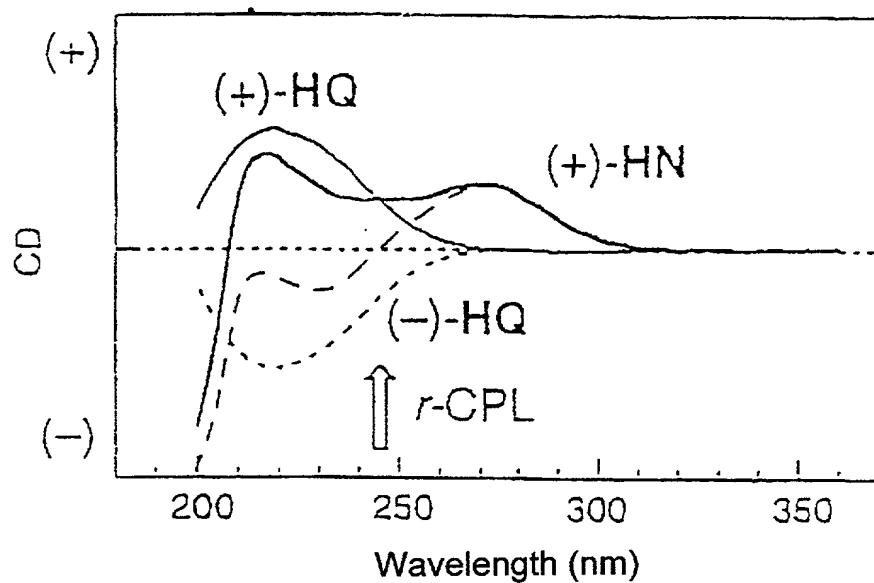


Fig. 13

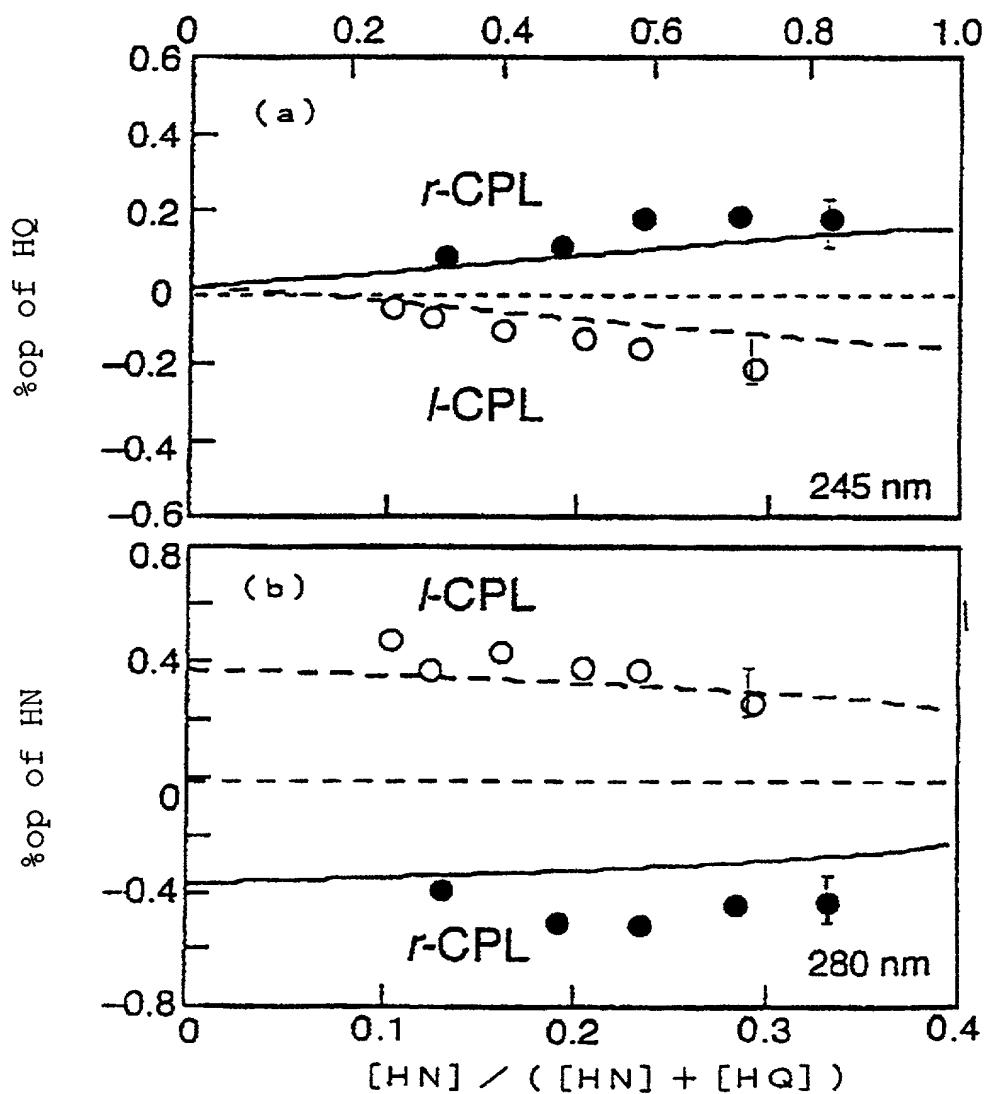
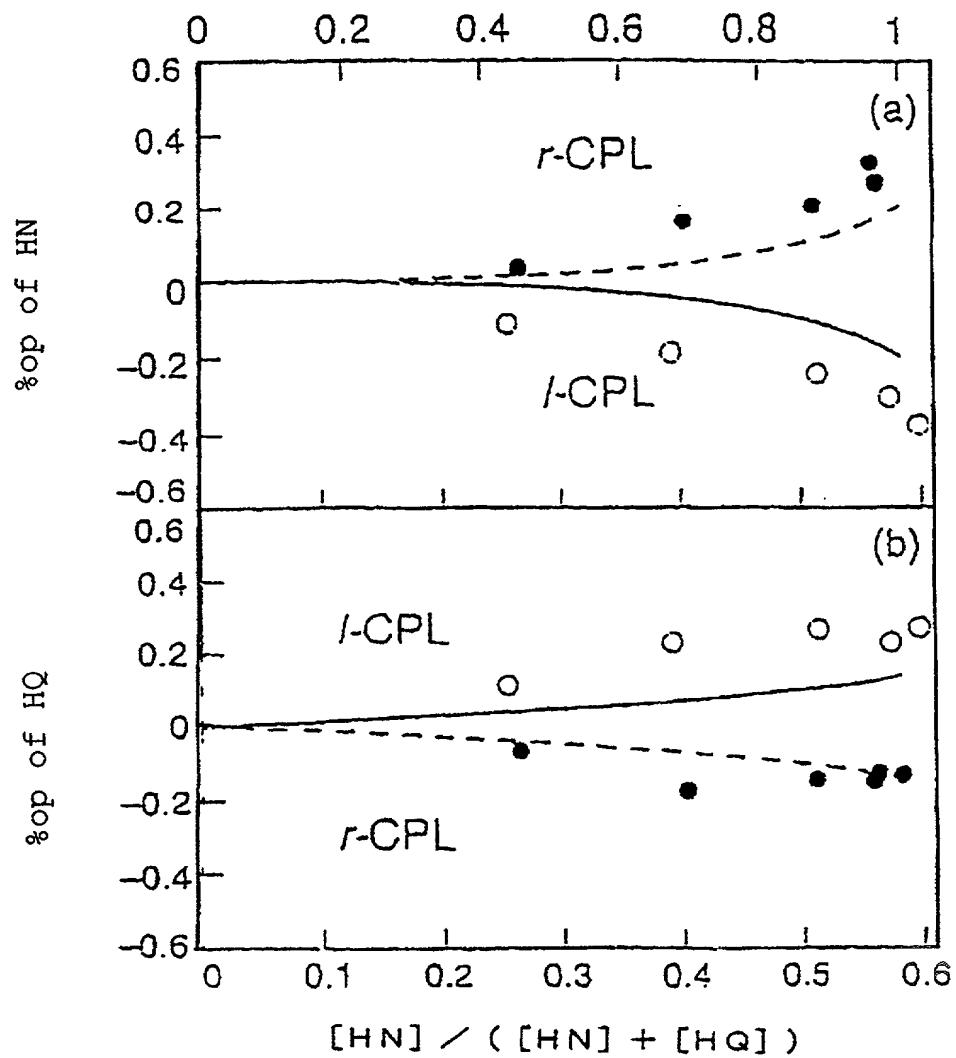


Fig. 14

 $[\text{HN}]/(\text{concentration of HN in the photostationary state})$ 

DECLARATION AND POWER OF ATTORNEY - USA PATENT APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name;

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is

sought on the invention entitled METHOD FOR ABSOLUTE ASYMMETRIC SYNTHESIS

the specification of which:

- (a) is attached hereto; or
- (b) was filed on _____ as Application No. _____ or Express Mail No., as Application No. not yet known _____ and was amended on _____ (if applicable); or
- (c) X was described and claimed in PCT International Application No. PCT/JP00/01561 filed on March 15, 2000 and as amended under PCT Article 19 on _____ (if any) and/or under PCT Article 34 on December 27, 2000 (if any).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above;

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, § 1.56;

I hereby claim foreign priority benefits under Title 35, United States Code, § 119 of any foreign application(s) for patent, design or inventor's certificate or any PCT international application(s) listed below and have also identified below any foreign application(s) for patent, design or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed for the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN APPLICATION(S)

COUNTRY (OR INDICATE IF PCT)	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 37 U.S.C. § 119	
Japan	1999-236171	23/08/1999	X YES	NO
			YES	NO
			YES	NO
			YES	NO

I hereby claim the benefit under Title 35, United States Code, § 120 of any United States application(s) listed below, and insofar as the subject matter of each of the claims of this application is not disclosed in the prior

United States application in the manner provided by the first paragraph of Title 35, United States Code § 112, I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56, which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Prior U.S.A. Application(s)

Application No.: _____ Filing Date: _____ Status: _____

POWER OF ATTORNEY: I hereby appoint the registrants of Knobbe, Martens, Olson & Bear, LLP, 620 Newport Center Drive, Sixteenth Floor, Newport Beach, California 92660, Telephone (949) 760-0404, Customer No. 20,995.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful, false statements may jeopardize the validity of the application or any patent issued thereon.

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Inventor's signature Hideo Nishino Day 12th Month February Year 2002

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PF-33